

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel Acino Pharma 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: each film-coated tablet contains 3.80 mg of hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, marbled, round and biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- 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.

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

- Adults and elderly
Clopidogrel should be given as a single daily dose of 75 mg.

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.
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- Paediatric population
 - Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).
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- 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.
- 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 nonsteroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors. 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, 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.

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 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).

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 Acino Pharma 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).

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).

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 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 H₂ 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 coadministration 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 products 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).

Breastfeeding

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.

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

Clopidogrel has been evaluated for safety for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE study are discussed below. Overall, clopidogrel 75 mg/day was comparable 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 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 1.6% for ASA.

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 ($< 1/10,000$). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
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
Immune system disorders				Serum sickness, anaphylactoid reactions
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	
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
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, rash erythematous, urticaria, eczema, lichen planus
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		

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.

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 P2Y₁₂ 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.

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.

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 ≤ 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.

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 μ M ADP-induced platelet aggregation) which was comparable to that of adults taking Plavix 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.

Metabolism

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 ^{14}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 μ 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 μ 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.

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:

Macrogol 6000
Cellulose, microcrystalline (E460)
Crospovidone type A
Castor oil, hydrogenated

Film-coating:

Macrogol 6000
Ethylcellulose (E462)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu/Alu blisters containing 14, 28, 30, 50, 84, 90 and 100 film-coated tablets packed in cardboard cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Acino Pharma GmbH
Am Windfeld 35
83714 Miesbach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/549/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21.09.2009

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/>

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

Medicinal product no longer authorised

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Acino AG
Am Windfeld 35
83714 Miesbach
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

Not applicable.

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

PSURs

The PSUR submission schedule should follow the PSUR schedule for the reference product.

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

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel Acino Pharma 75 mg film-coated tablets
Clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
84 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Acino Pharma GmbH
Am Windfeld 35
83714 Miesbach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/549/001
EU/1/09/549/002
EU/1/09/549/003
EU/1/09/549/004
EU/1/09/549/005
EU/1/09/549/006
EU/1/09/549/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Clopidogrel Acino Pharma 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel Acino Pharma 75 mg film-coated tablets

Clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Acino Pharma GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clpidogrel Acino Pharma 75 mg film-coated tablets Clpidogrel

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist,

In this leaflet:

1. What Clpidogrel Acino Pharma is and what it is used for
2. Before you take Clpidogrel Acino Pharma
3. How to take Clpidogrel Acino Pharma
4. Possible side effects
5. How to store Clpidogrel Acino Pharma
6. Further information

1. WHAT CLOPIDOGREL ACINO PHARMA IS AND WHAT IT IS USED FOR

Clpidogrel Acino Pharma contains the active ingredient Clpidogrel which belongs to a group of medicines called antiplatelet medicinal products. Platelets (so-called thrombocytes) are very small structures, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Clpidogrel Acino Pharma is taken to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Clpidogrel Acino Pharma to help prevent blood clots and reduce the risk of these severe events because:

- You have a condition of hardening of arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease (disturbed blood flow in arms or legs caused by vascular occlusions)

2. BEFORE YOU TAKE CLOPIDOGREL ACINO PHARMA

Do not take Clpidogrel Acino Pharma:

- If you are allergic (hypersensitive) to clpidogrel or any of the other ingredients of Clpidogrel Acino Pharma;
- 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 think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Clpidogrel Acino Pharma.

Take special care with Clopidogrel Acino Pharma:

If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel Acino Pharma:

- 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 within the last seven days
- if you have kidney or liver disease

While you are taking Clopidogrel Acino Pharma:

- You should tell your doctor if a surgery (including dental) is planned.
- 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 Acino Pharma is not intended for use in children or adolescents.

Taking other medicines

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

Some other medicines may influence the use of Clopidogrel Acino Pharma or vice versa.

You should specifically tell your doctor if you take

- oral anticoagulants, medicines used to reduce blood clotting,
- a 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
- 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.

Acetylsalicylic acid, a substance present in many medicines 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.

Taking Clopidogrel Acino Pharma with food and drink

Clopidogrel Acino Pharma may be taken with or without food.

Pregnancy and breast-feeding

It is preferable not to take this product during pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel Acino Pharma. If you become pregnant while taking Clopidogrel Acino Pharma, 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 Acino Pharma is unlikely to affect your ability to drive or to use machines.

Important information about some of the ingredients of Clopidogrel Acino Pharma:

Clopidogrel Acino Pharma contains hydrogenated castor oil which may cause stomach upset or diarrhoea.

3. HOW TO TAKE CLOPIDOGREL ACINO PHARMA

Always take Clopidogrel Acino Pharma exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one 75 mg tablet of Clopidogrel Acino Pharma per day to be taken orally with or without food, and at the same time each day.

You should take Clopidogrel Acino Pharma for as long as your doctor continues to prescribe it.

If you take more Clopidogrel Acino Pharma than you should

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

If you forget to take Clopidogrel Acino Pharma

If you forget to take a dose of Clopidogrel Acino Pharma, 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 the forgotten individual doses.

If you stop taking Clopidogrel Acino Pharma

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clopidogrel Acino Pharma can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)

- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data)

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 'Take special care with Clopidogrel Acino Pharma').
- 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 reported with clopidogrel 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 Acino Pharma.

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 'Take special care with Clopidogrel Acino Pharma').

Other side effects reported with Clopidogrel Acino Pharma are:

-Common side effects:

Diarrhoea, abdominal pain, indigestion or heartburn.

-Uncommon side effects:

Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

-Rare side effect:

Vertigo.

-Very rare side effects:

Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough, generalised allergic reactions; swelling in the mouth; blisters of the skin; skin allergy; inflammation of the mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in the way things taste.

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOPIDOGREL ACINO PHARMA

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

Keep out of the reach and sight of children.

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

Do not use Clopidogrel Acino Pharma if you notice any visible sign of damage of blister or film-coated tablets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Clopidogrel Acino Pharma contains

The active substance is clopidogrel. Each tablet contains 75 mg of clopidogrel (as besilate).

The other ingredients are:

Tablet core:

Macrogol 6000
Cellulose, microcrystalline (E460)
Crospovidone type A
Castor oil, hydrogenated

Film-coating:

Macrogol 6000
Ethylcellulose (E462)
Titanium dioxide (E 171)

What Clopidogrel Acino Pharma looks like and contents of the pack

Clopidogrel Acino Pharma 75 mg film-coated tablets are white to off-white, marbled, round and biconvex. They are supplied in cardboard cartons containing 14, 28, 30, 50, 84, 90 and 100 tablets in aluminium blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Acino Pharma GmbH
Am Windfeld 35
83714 Miesbach
Germany

Manufacturer

Acino AG
Am Windfeld 35
83714 Miesbach
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in.

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