Clopidogrel-Acino 75, film-coated tablets

Composition

Active ingredient: Clopidogrelum ut Clopidogreli besilas.

Excipients: Macrogolum 6000, Carbonei dioxidum, Cellulosum microcristallinum (E 460), Crospovidonum, Ricini oleum hydrogenatum, Ethylcellulosum, Titanium dioxide.

Galenic Form and Active Ingredient per Unit

On film-coated tablet contains 111,85 mg Clopidogrel besilate (corresponding to 75 mg Clopidogrel).

Indications / Possibilities of Use

Prevention of atherothrombotic events as myocardial infarction, ischemic stroke, vascular induced death in patients with recent stroke (form 7 days until less than 6 months), recent infarct (from a few days until less than 5 weeks) or manifest peripheral artery occlusive disease (PAOD).

In combination with ASA in patients with acute coronary syndrome without ST segment elevation (unstable angina pectoris or Non-Q-wave-infarction).

In combination with ASA after fibrinolysis in acute myocardial infarction with ST segment elevation.

Clopidogrel is used in combination with ASA for the prevention of thrombotic events after stent placement.

Dosage / Use

Clopidogrel-Acino is used once daily, with or without food.

Prevention atherothrombotic events

Once daily 1 film-coated tablets (corresponding to 75 mg Clopidogrel-Acino).

Acute coronary syndrome and stent

Acute coronary syndrome without ST segment elevation: Clopidogrel-Acino treatment is started with a loading dose of 300 mg (4 tablets à 75 mg) and then continued at 75 mg once a day for long term treatment (in combination with daily 75–325 mg ASA).

In ST segment elevation acute myocardial infarction after fibrinolysis: 1 tablet of Clopidogrel-Acino 75 once a day with or without loading dose in combination with ASA (see «Properties/ Effects»).

Children and adolescents

The safety and efficacy in children and adolescents below 18 years has not yet been established.

Renal and hepatic impairment

A dosage adjustment in elderly patients is not necessary (see «Pharmacokinetics»). Therapeutic experience is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore clopidogrel should be used with caution in these patients.

CYP2C19 poor metaboliser

The weak metabolism through CYP2C19 is connected to a decreased effect of clopidogrel. The optimal dosage has not yet been determined in those patients.

Contraindications

Hypersensitivity to the active substance or to any of the excipients; history of allergic reactions to ticlopidine.

Organ lesions with bleeding tendencies: e.g. active gastrointestinal ulcer, acute hemorrhagic stoke.

Severe liver impairment.

Hemorrhagic diatheses.

Warnings and Precautions

Thrombotic Thrombocytopenic Purpura (TTP) is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Due to the risk of bleeding and haematological undesirable effects, 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 «Undesired Effects»).

In view of the lack of data, clopidogrel cannot be recommended during the acute phase (first 7 days) after acute ischemic stroke.

Caution is indicated with inadequately treated or untreated hypertension.

As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding (particularly gastrointestinal and intraocular) from surgery, trauma or other pathological conditions.

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.
If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery.
Drugs which may cause gastrointestinal lesions (e.g. non-steroidal anti-inflammatory drugs) should be used with caution in patients treated with clopidogrel.
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. In additions, patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken.
In patients with TIA (transient ischemic attack) or cerebrovascular insults with a risk of recurrent ischemic events an increase of stronger bleedings has been reported when combining clopidogrel and aspirin. Therefore such a combination is to be used with caution in extra-clinical situations with proven benefit.
Clopidogrel should not be used after fibrinolytic treatment with streptokinase for the treatment of a recent myocardial infarct, as in such cases bleedings appeared more frequently than after other thrombolytic treatments.

Interactions

In addition to the below described interactions, patients which entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACE inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement medication and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.
Clopidogrel should be used with cautions in patients which are treated with ASA, non-steroidal anti-inflammatory drugs, heparin, GPIIb/IIIa antagonists or thrombolytics.
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 «Warnings and Precautions»). However, clopidogrel (75 mg per day after a loading dose of 300 mg) and ASA (75 to 325 mg per day) have been administered together for up to one year.

Injectable anticoagulats

In a clinical study with clopidogrel on volunteers it was not necessary to adjust the heparin dosage neither did clopidogrel influence the effect of heparin on the coagulation. Concomitant use of heparin did not have and influence on the clopidogrel-induced inhibition of platelet aggregation. However, the safety of concomitant use of clopidogrel and heparin has not been documented appropriately yet. Therefore, concomitant therapy should only be performed with caution.

Fibrinolytics

The safety 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. Concomitant administration of clopidogrel and fibrinolytics, especially streptokinase, should however be performed with caution (see «Warnings and Precautions»).

Oral Anticoagulants

In a placebo controlled study (clopidogrel vs. placebo/warfarin in patients with atrial fibrillation) the concomitant use of clopidogrel did neither change the pharmacodynamic (INR) nor the pharmacokinetic of warfarin.

The concomitant administration of clopidogrel with warfarin may increase the intensity of bleedings. Similar effects may not be excluded for other oral anticoagulants as phenprocoumon and acenocoumarol.

Non-Steroidal Anti-Inflammatory Drugs (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 and clopidogrel should be co-administered with caution (see «Warnings and Precaution»).

Interactions with other medicinal products

Data from in-vitro studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. Cytochromes 2D6, 3A4, 1A1, 2C19, 2E1 and 2A6 were not inhibited. Clopidogrel is a week inhibitor of CYP 2B6.

The in-vitro metabolism to generate the active metabolite involves CYP 3A4, CYP 2C19, CYP 1A2, CYP 2C9 und CYP 2B6. In a clinical study on health volunteers treated with a combination of 75 mg clopidogrel and 200 mg ketoconazol an increase of the inactive main metabolite of clopidogrel in the C_{max} and AUC of 1.15 and 1.5, respectively, has been shown.

This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with

clopidogrel.
In vitro (liver microsomes) the formation of the active metabolite is increased under rifampicin and there is still an inhibition of erythromycin. In what extent incuctors or inhigibors influcnece the clinical effect of clopidogrel is not known todate; the concomitant use should be performed with caution. In particular, medicine which are at the same time inhibitors of CYP 2C9 und CYP 3A4, as amiodarone, fluconazole, voriconazole, miconazole, imatinib and delavirdine, should be avoided. The pharmacodynamic of clopidogrel was not altered significantly by co-administraion of phenobarbital (inducer of CYP 3A4). The absorption of clopidogrel is increades by the inhibiors of MDR1 (p-Gp). A comedication of MDR-1 inhibitors as ciclosporin, verapamil and chinidin should therefore occur with caution.
As data from literature shows, patients with a genetic acquired functional impairment of CYP 2C19 are systemic seen less exposed to the active metabolite of clopidogrel. Compared to patients with a normal CYP 2C19 function these patients have a reduced inhibition of platelet aggregation as well as in general a higher incidence of cardiovascular events inclusive MI and stent thrombosis.
As the metabolism of clopidogrel to the active metabolite is partly via CYP 2C19 the use of a medicine which inhibits the activity of the enzyme could decrease the concentration of the active metabolite of clopidogrel and therefore also the clinical efficacy. Therefore, the concomitant use of these medicines is not recommended. The following drugs which inhibit the CYP2C19 are cited: omeprazol, esomeprazol, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ciprofloxacin, cimetidine, carbamazepine, oxcarbamazepine and chloramphenicol. In case a proton-pump inhibitor is to be administered it is recommended to choose a weak CYP2C19 inhibitor such as pantoprazol. Furthermore antacids do not have any influence on the absorption of clopidogrel.
Patients with a genetically caused reduction of CYP2C19 function (poor metaboliser) have an active rate of metabolites which are 70% lower than in patients with normal CYP2C19 function as well as a reduced inhibition of the platelet aggregation. Form this they may experience a higher incidence of cardiovascular events, including myocardial infarct and stent thrombosis.
No clinically significant pharmacodynamic interaction has been observed when clopidogrel was used concomitantly with atenolol, nifedipine or both together. Neither did the concomitant use of phenobarbital, cimetidine or estrogens have a significant effect on the pharmacodynamic of clopidogrel. In addition, clopidogrel did not alter the pharmacodynamic (INR) nor the pharamokinetic of warfarin (a sensitive substrate of isoenzyme 2C9) when administered together in an interaction study.
The concomitant use of clopidogrel did not have any influence on the pharmacokinetic of digoxin or theophylline. Antacids did not alter the resorption rate of clopidogrel.

Pregnancy / Lactation

Studies on reproduction have been performed in rats with dosages up to 500 mg/kg per day and in rabbits with doses up to 300 mg/kg per day. There were not indications on the impairment of clopidogrel on fertility or harmfulness on the foetus. However, no clinical data on exposure to clopidogrel during pregnancy are available As the results of animal studies on reproduction can not always be transferred to humans; the use of clopidogrel during pregnancy should only occur upon mandatory indication.

Animal studies on rats have shown excretion of clopidogrel and/or its metabolites in breast milk. Analogue experiences on the excretion of the drug in breast milk in women do not exist. During treatment with clopidogrel, breast feeding should not be continued.

Effects on ability to drive and use machines

During the treatment with clopidogrel no influence on the ability to drive and to use machines or on the psychometric capacity has been observed.

Undesirable Effects

Clopidogrel has been evaluated for safety in more than 42,000 patients. Over 9,000 patients were treated for 1 year or more with the medicinal product. The clinically relevant adverse reactions have been observed in the controlled clinical studies. The first study compared clopidogrel with ASA in a dosage of 325 mg per day. In the other studies clopidogrel was combined with ASA in a dosage of 75-325 mg per day.

Regardless of age, gender and race, clopidogrel 75 mg/day was well tolerated compared to ASA 325 mg/day in the CAPRIE study. In patients treated with clopidogrel, the overall incidence of any bleeding was 9.3%. The incidence of major bleedings was 1.4%, the incidence of gastrointestinal bleedings was 2.0%, whereat in 0.7% of the cases a hospitalisation revealed necessary. The incidence of intracranial bleeding was 0.4%.

CURE: compared to the administration of placebo-ASA the combination of clopidogrel+ASA was not associated to a statistical significant increase of life-threatened or deathly bleedings (rate of incidence 2,2% vs. 1,8% and 0,2% vs. 0,2%). The incidence of intracranial bleeding was of 0.1% vs. 0.1%, the incidence of major bleedings was 1.6% vs. 1.0%, gastrointestinal bleedings or bleeding in the region of the sites of punctures as well as minor bleeding 5.1% vs. 2.4%. There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped an antithrombotic therapy more than five days prior to surgery.

In CLARITY, the incidence of major bleedings was similar between the observed groups (1.3% versus 1.1% for the clopidogrel+ASA and the placebo+ASA groups, respectively). The inci-

dence of deathly bleedings (0,8% vs. 0,6% for clopidogrel+ASA and placebo+ASA, respectively) and intracranial bleeding (0,5% vs. 0,7% for clopidogrel+ASA and placebo+ASA, respectively) was low and in both groups similar.

The undesired effects are listed according to organ class and frequency. Their frequency is defined using the following conventions: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

The listed undesired effects with a very rare incidence were observed during Post-marketing studies, the undesired effects with higher incidence were observed in clinical studies.

Immune system disorders

Very rare*:* anaphylactoid reactions, serum sickness, angioedema.

Hematologic disorders

Uncommon*:* leucopenia, eosinophilia, bleeding time prolonged and platelet count decreased.

Rare*:* severe neutropenia (<0,45x 10^9/l), thrombocytopenia (<80x 10^9/l).

Very rare*:* aplastic anaemia, agranulocytosis, pancytopenia, severe thrombocytopenia (≤30x 10^9/l), TTP.

Bleeding disorders

Common*:* bleedings and severe cases of gastrointestinal haemorrhage (occasional requireing hospitalisation), purpura, bruising and haematoma.

Very rare*:* severe cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage) and of haematuria and haemorrhage of operative wound. Some cases with fatal outcome have been reported (especially intracranial, gastrointestinal and retroperitoneal bleeding).

Central and peripheral nervous system disorders

Uncommon*:* headache, dizziness and paraesthesia.

Rare*:* vertigo.

Very rare*:* taste disorders.

Psychiatric disorders

Very rare*:* confusion, hallucinations.

Vascular disorders

Very rare*:* vasculitis, hypotension.

Respiratory, thoracic and mediastinal disorders

Very rare*:* bronchospasm, interstitial pneumonitis.

Gastrointestinal disorders

Common*:* dyspepsia, abdominal pain and diarrhoea.

Uncommon*:* nausea, gastritis, flatulence, constipation, vomiting, Gastric ulcer and duodenal ul-

cer.
Very rare*:* colitis, pancreatitis, stomatitis.
Hepato-biliary disorders
Very rare*:* hepatitis, acute liver failure.
Skin and subcutaneous tissue disorders
Common*:* rash.
Uncommon*:* pruritus.
Very rare*:* bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), rash erythematous, rash makulous, urticaria, rash, lichen ruber planus.
Musculoskeletal disorders
Very rare*:* arthralgia, arthritis, myalgia.
Renal and urinary disorders
Very rare*:* glomerulonephritis, blood creatinine increased.
General disorders and administration site conditions
Very rare*:* fever.
In very rare cases thrombotic thrombocytopenic purpura (TTP) has been reported; in some cases shortly after administration. The appearance of thrombopenia and of haemolytic microangiophatic anaemia associated to neurological disorders, renal impairment or fever is characteristic for this disease.

Overdose
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications.
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.

Properties / Effects
ATC-Code: B01AC04
Mode of action
Clopidogrel is a prodrug that is metabolised by the CPY450 enzyme in order be transformed into the active metabolite which is inhibiting the platelet aggregation. This occurs by selectively inhibiting the binding of the adenosine diphosphate (ADP) to the platelet receptor $P2Y_{12}$ and the subsequent ADP-mediated activation of the GPIIb/IIIa complex. The platelet aggregation by other agonists as ADP is also inhibited by neutralised the amplification of platelet activation by released ADP.
Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets ex-

posed to clopidogrel are affected for the remainder of their lifespan (ca. 7–10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover.
As the active metabolite is formed by the CYP450 enzymes (some of those underlie to a genetic polymorphism or may be inhibited by other medicines) not all the patients will experience a satisfactory inhibition of platelet aggregation (see «Interactions» and «Pharmacokinetic: Pharmacogenetic»).
A statistically significant and dose-dependent inhibition of platelet aggregation has been observed 2 hours after as single oral dose of clopidogrel. 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%.
Using a loading dose of 300 mg this inhibition (55%) was reached within the first hour and maintained by daily 75 mg clopidogrel.
Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days after treatment was discontinued.
Clinical studies
The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischemic 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 (medium 1,6 years).
Clopidogrel significantly reduced the incidence of new ischemic events (combined end point of myocardial infarction, ischemic 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). 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, ischemic 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). 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). 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.

The CURE study included 12,562 patients with 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 ischemia. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo, both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. Medium treatment time was 9 months.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was significantly reduced by concomitant administration of clopidogrel and ASA. In the clopidogrel-treated group they were 582 (9.3%) and in the pla- cebo-treated group 719 (11.4%); meaning a 20% relative risk reduction (p <0,001) for the clopidogrel-treated group. The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischemia) 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 (p=0.001) for the clopidogrel-treated group.

Patients (2'253) with coronary revascularization (chirurgical or percutaneous with or without stent implantation) showed a similar significant benefit with clopidogrel + ASA compared to ASA alone (p= 0,002).

This benefit was mostly driven by the statistically significant reduction in the incidence of MI. The differences related to stroke, cardiovascular death and overall mortality were not significant.

The observed risk reduction was consistent over the whole patient population. In the non-smoker group the observed efficacy was lower than in the smoker and ex-smoker group, respectively. In a multiple analysis of variance with other decisive risk factors the incidence rate(95% CI) was 0,62 (0,48, 0,81) in patients still smoking, 0,76 (0,64, 0,90) in ex-smokers and 0,94 (0,79, 1,11)in those which have never smoked.

The efficacy of clopidogrel was independent of the ASA dose (75–325 mg daily).

In the CLASSICS study the tolerance of clopidogrel in combination with aspirin after a coronary stent implantation has been investigated. The following three groups have been compared: clopidogrel 75 mg, clopidogrel 300 mg the first day followed by 75 mg daily and ticlopidine 250 mg twice daily. In addition, all three groups received 325 mg ASA for 28 days. Events with the primary endpoints «local vascular complications with severe bleeding, neutropenia, thrombocytopenia or premature dropout due to non-cardiac side effects»: 4,56% for clopidogrel with or without loading dose/ASA and 9,12% for ticlopidine/ASA. The difference was statistical significant (p= 0,005). The incidence of sever cardiac events (secondary endpoints: MI, death due to cardiovascular reasons and a coronary re-intervention) was not statically significant different in each of the three groups.

The tolerance and efficacy of clopidogrel in patients being in the acute phase of a myocardial infract with ST elevation has been investigated in a randomised, placebo-controlled, double-blind study.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. 45 minutes after the thrombolytic treatment (streptokinase, alteplase, reteplase, tenecteplase) patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1752) 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 GP IIb/IIIa antagonists 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. Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint (p <0,0001, OR 0,64/0,53 vs. 0,76, respectively).

Pharmacokinetic

Absorption

After oral intake of 75 mg per day, clopidogrel is rapidly absorbed and the mean peak plasma peaks of the unmodified clopidogrel are reached approx. 45 minutes after intake. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution

Clopidogrel and the main circulating 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. A minor part is bound irreversible.

Metabolism

Clopidogrel is a prodrug which is metabolised by the liver. In vitro and in vivo clopidogrel is metabolised via two main pathways: on one side clopidogrel is hydrolysed by esterase's producing an inactive carboxyl acid derivate (85% of the circulating metabolites) and on the other side a second pathway is mediated by multiple cytochromes P450. Clopidogrel is first metabolised to 2-oxo-clopidogrel intermediate. The subsequent metabolisation results in formation of the active metabolites (a thiol derivate of clopidogrel). In vitro this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6.

The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The C_{max} and AUC of the main circulating metabolite were linear in the dose range of 50 to 150 mg of clopidogrel.

In-vitro studies on human liver microsomes have shown that the carboxyl acid metabolite of clopidogrel is inhibiting the enzymatic activity of Cytochrom P450 2C9; Cytochroms 2D6, 3A4, 1A1, 2C19, 2E1 and 2A6 were not inhibited. In an interaction study with warfarin, a 2C9-isoenzym sensitive substrate, clopidogrel did not alter the pharmacodynamic (INR) or the pharmacokinetic of warfarin. Therefore an in-vivo inhibition of the isoenzyms of P450 (inclusively 2C9) and a consecutive metabolic interaction with clopidogrel are not being expected.

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 exhibits a half-life of approx. 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

The pharmacokinetic of the active metabolite of clopidogrel and the platelet aggregation inhibiting effect (measured by ex vivo platelet aggregation assay) differs dependent on the CYP2C19 genotype. The CYP2C19*1 allele corresponds to the full functional metabolism, the CYP2C19*2 and CYP2C19*3 alleles correspond to a reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles make up 85% of the white population and 99% of the Asian population with reduced function. Other alleles which are also associated to a reduced metabolism include CYP2C19*4, *5, *6, *7 and *8 but those occur less frequent in the global population.

The published frequencies of the frequent CYP2C19 phenotypes and genotypes are listed below: the «extensive metabolisers» (CYP2C19*1/*1) make up 74%, 66% and 38% of the white, the black and the Chinese population, respectively. The «intermediate metabolisers» (CYP2C19*1/*2 or *1/*3) make up 26%, 29% and 50% of the white, the black and the Chinese population, respectively. And the «poor metabolisers» (CYP2C19*2/*2, *2/*3 or *3/*3) make up 2%, 4% and 14% of the white, the black and the Chinese population, respectively.

The reduced CYP2C19 metabolism in intermediate and poor metabolisers lowers the C and the AUC of the active metabolite to about 30–50%.

Pharmacogenetic examination can identify genotypes which are associated to a variability of the CYP2C19 activity.

Kinetics of special groups of patients

The pharmacokinetic of the active metabolite of clopidogrel is not known in special groups of patients.

Elderly

The plasma concentrations of the circulating main metabolite were clearly higher. However, those higher plasma levels had not influence on the platelet aggregation or the bleeding time. No dosage adjustment is necessary for elderly patients.

Renal impairment

After repeated clopidogrel administration of 75 mg per day to patients with severe renal impairment (creatininr clearance of 5-15 minutes) the inhibition of the ADP-induces platelet aggregation was lower 825%) than in persons with normal renal function. However the prolongation of the bleeding time was similar to the one of persons with normal renal function which were also taking 75 mg per day.

Hepatic impairment

Clopidogrel C_{max} for both single dose and steady state for cirrhotics (Child Pugh A or B) was many folds higher than in normal subjects. Cirrhotics also showed minor elevation of plasma-levels of the main metabolite (AUC). Patients with severe liver cirrhosis have not been investigated. After repeated administration of 75 mg clopidogrel per day over a period of 10 days in patients with severe hepatic impairment the inhibition of ADP-induced platelet aggregation was similar to the one in healthy persons. Mean bleeding time was also comparable in both groups.

Race

See «Pharmacokinetic: Pharmacogenetic».

Preclinical 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).

Further, clopidogrel showed no genotoxic activity in appropriate investigations.

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 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 due to its bad taste.

Other indications

Shelf-life

The pharmaceutical product may only be used up to the expiration date indicated on the package with «EXP».

Special storage instructions

Do not store above 25°C and protect from humidity in the original packaging.

Marketing Authorisation Number

60’101 (Swissmedic)

Packaging

Clopidogrel-Acino 75: 28, 84 film-coated tablets (B)

Marketing Authorisation Holder

Acino Pharma AG, Liesberg

Status of Information

November 2010