SUMMARYOFPRODUCTCHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Antiplatt 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mgof clopidogrel (as clopidogrel bisulfate).

*Excipients with known effect:*Lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Light pink colored, round, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention ofatherothrombotic events
Clopidogrel is indicated in:

- Adult patients sufferingfrom myocardial infarction (from a few days until less than 35 days), ischemic stroke (from7 days until less than 6 months) or established peripheral arterial disease.
- Adult patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acutecoronarysyndrome (unstable angina or non-Q-wavemyocardialinfarction), includingpatients undergoing a stent placement followingpercutaneous coronaryintervention, in combination with acetylsalicylicacid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

In patients with moderate to high-risk Transient Ischemic Attack(TIA) or minor Ischemic Stroke (IS)

Clopidogrel in combination with ASA is indicated in:

- Adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

Inadult patients with atrial fibrillation who haveat least onerisk factor for vascularevents, arenot suitablefor treatment with Vitamin K antagonists (VKA)and who havea low bleedingrisk, clopidogrel is indicated in combination with ASA for theprevention of atherothrombotic and thromboembolic events, includingstroke.

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 asingledailydose of75 mg.

  In patientssufferingfromacutecoronarysyndrome:

  - 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 or 600mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see section 4.4).Clopidogrel treatment should be 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 itis recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trialdata support use up to 12 months, and the maximum benefit was seen at3 months (see section 5.1).

[1]Age,Bloodpressure,Clinicalfeatures,Duration,andDiabetesmellitusdiagnosis
[2]National Institutes of Health Stroke Scale

- 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 incombination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without aloading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of thecombination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1).

Adultpatientswithmoderateto high-riskTIAorminorIS:

Adult patients with moderate to high-riskTIA (ABCD2 score ≥4)orminor IS (NIHSS≤3)should be given a loadingdose of clopidogrel 300mgfollowed byclopidogrel75 mgonce dailyand ASA (75 mg -100mgonce daily).Treatment withclopidogreland ASA should bestartedwithin 24 hoursoftheevent andbe continuedfor21 days followedbysingleantiplatelettherapy.

In patients with atrialfibrillation, clopidogrelshould be given as a single dailydose of75 mg. ASA (75-100 mgdaily) should beinitiated andcontinued incombinationwith clopidogrel(seesection5.1).

Ifadoseismissed:

- 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 beusedin childrenbecauseofefficacyconcerns(seesection 5.1).

- Renalimpairment

  Therapeuticexperienceislimitedinpatientswithrenalimpairment(seesection4.4).

- Hepaticimpairment

  Therapeuticexperienceislimited in patients with moderate hepaticdisease whomay havebleedingdiatheses(seesection 4.4).

<u>Method ofadministration</u>

For oral use

Itmaybe given with or withoutfood.

4.3 Contraindications

- Hypersensitivityto theactivesubstanceor toanyof the excipients listed in section 2 or section 6.1.
- Severehepaticimpairment.
- Active pathological bleedingsuchas peptic ulceror intracranial hemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological disorders

Dueto therisk ofbleeding andhaematologicaladversereactions,bloodcellcount determination and/or otherappropriate testing shouldbepromptlyconsideredwheneverclinicalsymptomssuggestiveofbleedingariseduringthecourseoftreatment(seesection4.8). As with other antiplateletagents, clopidogrelshould be used with caution in patients who maybeatriskofincreasedbleedingfromtrauma,surgeryorotherpathologicalconditionsandinpatientsreceivingtreatmentwithASA,heparin,glycoproteinIIb/IIIainhibitorsornon-steroidalanti-inflammatory drugs(NSAIDs)including Cox-2inhibitors, or selective serotoninreuptakeinhibitors(SSRIs),orCYP2C19stronginducersorothermedicinal productsassociatedwithbleeding risk suchaspentoxifylline (seesection4.5). Duetothe increasedrisk ofhaemorrhage,tripleantiplatelet therapy (clopidogrel+ASA+dipyridamole) forstrokesecondary preventionisnotrecommendedinpatientswithacutenon-cardioembolic ischemicstrokeor TIA(seesection4.5andsection4.8).Patientsshouldbefollowedcarefully forany signsofbleeding including occultbleeding,especially during thefirstweeksof treatment and/orafter invasivecardiacprocedures orsurgery. Theconcomitantadministration ofclopidogrelwith oralanticoagulants is not recommendedsinceitmay increase the intensity of bleedings(see section4.5).

Ifapatientistoundergoelectivesurgery andantiplateleteffectistemporarily notdesirable, clopidogrelshouldbediscontinued7 dayspriortosurgery.Patientsshouldinformphysicians anddentists thatthey are taking clopidogrel before any surgery is scheduledandbefore any newmedicinalproductistaken.Clopidogrelprolongsbleeding timeandshouldbeusedwith cautioninpatientswhohavelesionswithapropensitytobleed(particularlygastrointestinal and intraocular).

Patientsshouldbe told thatitmighttakelongerthan usual to stop bleeding whenthey take clopidogrel(aloneor in combination withASA), andthat they shouldreport any unusual bleeding(site orduration)to theirphysician.
Theuseofclopidogrel600mgloadingdoseisnot recommendedinpatientswithnon-ST segmentelevationacutecoronary syndromeand ≥75yearsofageduetoincreasedbleeding riskinthispopulation.

Thrombotic Thrombocytopenic Purpura (TTP)
ThromboticThrombocytopenicPurpura(TTP)hasbeenreportedveryrarelyfollowingthe useofclopidogrel,sometimesafterashortexposure.Itischaracterisedby thrombocytopenia andmicroangiopathichaemolyticanaemiaassociated witheitherneurologicalfindings,renal dysfunctionorfever.TTPisapotentially fatalconditionrequiring prompttreatmentincluding plasmapheresis.

Acquired haemophilia
Acquiredhaemophiliahasbeenreportedfollowinguseofclopidogrel.Incasesofconfirmedisolateda ctivatedPartial Thromboplastin Time(aPTT)prolongationwithorwithoutbleeding, acquiredhaemophiliashouldbeconsidered.Patients withaconfirmeddiagnosisofacquired haemophiliashouldbemanagedandtreatedby specialists,and clopidogrelshouldbe discontinued.

Recentischemicstroke

- *Initiation of therapy*
    - In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
    - There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
    - In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.
- *Non-minor IS patients (NIHSS >4)*

Inviewofthelackofdata,useofdualantiplatelettherapyisnotrecommended(see section4.1).

- *Recent minor IS or moderate to high-riskTIAinpatientsforwhom interventionis indicated or planned*

  Thereisnodata tosupporttheuseofdualantiplatelettherapy inpatientsforwhom treatmentwithcarotidendarterectomy orintravasculartherapy.Dualantiplatelettherapy isnot recommendedinthesesituations.

Cytochrome P4502C19 (CYP2C19)

Pharmacogenetics: Inpatients who are poor CYP2C19 metabolisers, clopidogrelat recommendeddosesformslessoftheactivemetaboliteofclopidogrelandhasasmallereffecton plateletfunction.Tests are availableto identifya patient'sCYP2C19 genotype.

SinceclopidogrelismetabolisedtoitsactivemetabolitepartlybyCYP2C19,use ofmedicinal productsthatinhibittheactivity ofthisenzymewouldbeexpectedtoresultin reduceddrug levelsoftheactivemetaboliteofclopidogrel. The clinicalrelevanceofthisinteraction is uncertain.As aprecaution concomitantuseofstrong ormoderateCYP2C19inhibitors should bediscouraged(seesection4.5foralistofCYP2C19 inhibitors,seealso section 5.2).

Useof medicinalproducts that induce the activity ofCYP2C19would be expectedto resultin increaseddrug levelsofthe activemetabolite ofclopidogrelandmightpotentiate thebleeding risk.AsaprecautionconcomitantuseofstrongCYP2C19inducersshouldbediscouraged (seesection 4.5).

CYP2C8 substrates

CautionisrequiredinpatientstreatedconcomitantlywithclopidogrelandCYP2C8substrate medicinalproducts(seesection4.5).

Cross-reactionsamong thienopyridines

Patientsshouldbeevaluatedforhistory ofhypersensitivity tothienopyridines(suchas clopidogrel, ticlopidine, prasugrel)since cross-reactivity among thienopyridineshas been reported(seesection4.8).Thienopyridinesmay causemildto severeallergicreactionssuchas rash, angioedema, or haematologicalcross-reactions such as thrombocytopaenia and neutropaenia.Patientswho haddevelopedaprevious allergicreactionand/orhaematological reactionto onethienopyridinemay haveanincreasedrisk ofdeveloping thesameoranother

reactiontoanotherthienopyridine.Monitoring forsignsofhypersensitivity inpatientswitha knownallergytothienopyridinesisadvised.

Renalimpairment

Therapeuticexperiencewithclopidogrelislimitedinpatientswithrenalimpairment. Therefore clopidogrelshould be used with cautioninthese patients (seesection 4.2).

Hepaticimpairment

Experienceislimitedinpatientswithmoderatehepaticdiseasewhomayhavebleeding diatheses.Clopidogrelshouldthereforebeusedwithcautioninthispopulation(seesection4.2).

Excipients

Antiplattcontainslactose.Patientswithrarehereditaryproblemsofgalactoseintolerance,total lactasedeficiencyorglucose-galactosemalabsorption shouldnottakethismedicinalproduct.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinalproducts associated with bleeding risk:There isan increased riskof bleedingdue tothepotentialadditiveeffect.Theconcomitantadministrationofmedicinalproducts associated withbleedingriskshould be undertaken with caution(see section4.4).

*Oral anticoagulants:*the concomitantadministration ofclopidogrel with oralanticoagulantsis not recommended sinceitmayincreasetheintensity ofbleedings(seesection 4.4). Although theadministrationofclopidogrel75mg/daydidnotmodifythepharmacokineticsofS-warfarinorInternationalNormalisedRatio(INR)inpatientsreceivinglong-termwarfarin therapy, coadministrationofclopidogrel with warfarinincreasestheriskof bleedingbecauseofindependenteffectsonhemostasis.

*GlycoproteinIIb/IIIainhibitors:*clopidogrelshould beused with cautionin patientswho receiveconcomitantglycoproteinIIb/IIIainhibitors(seesection4.4).

*Acetylsalicylic acid (ASA):*ASA did notmodifythe clopidogrel-mediatedinhibition of ADP-inducedplateletaggregation,butclopidogrelpotentiated the effect ofASA on collagen- induced platelet aggregation. However, concomitant administration of500 mgof ASA twicea dayforonedaydidnotsignificantlyincreasetheprolongationofbleedingtimeinducedby clopidogrelintake. A pharmacodynamic interaction betweenclopidogreland acetylsalicylic acidis possible,leadingtoincreasedriskof bleeding. Therefore, concomitantuse should be undertaken with caution(seesection 4.4). However, clopidogrel and ASA havebeen administered togetherfor up tooneyear(seesection5.1).

Heparin:inaclinicalstudyconductedinhealthysubjects,clopidogreldidnotnecessitate modification oftheheparindose oralterthe effectof heparin oncoagulation. Co-administrationof heparin had no effecton the inhibitionofplateletaggregationinducedby clopidogrel. A pharmacodynamic interaction betweenclopidogrelandheparinis possible, leadingtoincreased riskofbleeding. Therefore,concomitant use should beundertaken with caution(seesection 4.4).

Thrombolytics:thesafetyof the concomitant administration ofclopidogrel,fibrinornon-fibrinspecificthrombolyticagentsandheparinswasassessedinpatientswithacute myocardial infarction.Theincidenceof clinicallysignificantbleedingwas similarto thatobserved when thrombolyticagentsand heparin areco-administered with ASA (see section4.8)

NSAIDs:inaclinicalstudyconductedinhealthy volunteers,theconcomitantadministrationof clopidogrelandnaproxenincreasedoccultgastrointestinalbloodloss.However, duetothelackofinteractionstudieswithotherNSAIDsitispresentlyunclearwhetherthereisanincrea sed riskof gastrointestinalbleedingwith all NSAIDs. Consequently, NSAIDs includingCox-2inhibitorsandclopidogrelshouldbeco-administeredwithcaution(seesection4.4).

SSRIs:sinceSSRIsaffectplateletactivationandincreasetheriskofbleeding,theconcomitant administrationof SSRIswith clopidogrel shouldbe undertaken with caution.

Otherconcomitanttherapy:
Inducers of CYP2C19

Sinceclopidogrelismetabolisedto itsactivemetabolitepartlybyCYP2C19,useofmedicinalproductsthatinducetheactivityofthisenzymewouldbeexpectedto resultinincreaseddrug levelsoftheactivemetaboliteofclopidogrel.

Rifampicin stronglyinduces CYP2C19, resultingin both anincreasedlevel ofclopidogrel activemetaboliteandplateletinhibition,whichinparticularmightpotentiatetheriskof bleeding. As a precaution, concomitantuseofstrongCYP2C19 inducersshould be discouraged(seesection 4.4).

Inhibitorsof CYP2C19
Sinceclopidogrelismetabolisedto itsactivemetabolitepartlybyCYP2C19,useofmedicinal productsthatinhibittheactivityofthisenzymewouldbeexpectedto resultinreduceddruglevelsoftheactivemetaboliteofclopidogrel.Theclinicalrelevanceofthisinteractionisuncertain. Asa precautionconcomitantuse ofstrong ormoderateCYP2C19 inhibitors should be discouraged (seesections4.4 and 5.2).

MedicinalproductsthatarestrongormoderateCYP2C19 inhibitors include,forexample, omeprazole andesomeprazole,fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton PumpInhibitors(PPI):
Omeprazole80mgoncedailyadministeredeitheratthesametimeasclopidogrelorwith12 hoursbetweenthe administrationsofthetwo drugs decreasedthe exposure ofthe activemetabolite by45% (loadingdose)and 40%(maintenance dose).The decrease wasassociated with a39%(loadingdose)and 21% (maintenance dose) reduction ofinhibition ofplateletaggregation.Esomeprazoleisexpectedtogiveasimilarinteractionwithclopidogrel.

Inconsistentdataontheclinicalimplicationsofthispharmacokinetic(PK)/pharmacodynamic (PD)interactionin termsofmajorcardiovascularеventshavebeenreportedfromboth observationaland clinical studies. Asa precaution, concomitant use ofomeprazoleor esomeprazole should be discouraged(seesection 4.4).

Less pronouncedreductionsof metaboliteexposurehas beenobserved with pantoprazoleor lansoprazole.
Theplasmaconcentrationsoftheactivemetabolitewas20%reduced(loadingdose)and14%reduced(maintenancedose)duringconcomitanttreatmentwithpantoprazole80mgonce daily. This wasassociatedwith areductionofthe mean inhibition ofplateletaggregation by15% and 11%, respectively. Theseresultsindicatethatclopidogrelcanbe administered withpantoprazole.

Thereis no evidencethatother medicinal productsthatreduce stomach acid such asH2 blockersorantacidsinterferewithantiplateletactivityofclopidogrel.

Boosted anti-retroviral therapy(ART):HIV patientstreatedwith boosted anti-retroviral therapies(ART)areathigh-riskofvascularevents.

A significantlyreduced plateletinhibition has beenshown in HIVpatientstreatedwith ritonavir- or cobicistat-boosted ART. Although the clinicalrelevance ofthesefindingsis uncertain,there havebeen spontaneousreports ofHIV-infected patientstreatedwith ritonavir boosted ART, who haveexperienced re-occlusive events after de-obstruction orhavesuffered thromboticeventsunderaclopidogrelloadingtreatmentschedule.Averageplateletinhibition canbedecreasedwithconcomitantuseofclopidogrelandritonavir.Therefore,concomitant use ofclopidogrelwith ARTboostedtherapiesshouldbe discouraged.

Other medicinal products:A number of otherclinicalstudieshavebeenconducted with clopidogrelandotherconcomitantmedicinalproductstoinvestigatethepotentialfor pharmacodynamicandpharmacokineticinteractions.Noclinicallysignificant pharmacodynamic interactions wereobserved whenclopidogrel wasco-administered with atenolol,nifedipine,orbothatenololandnifedipine. Furthermore, the pharmacodynamic activityofclopidogrelwasnotsignificantlyinfluencedbytheco-administrationof phenobarbitaloroestrogen.

Thepharmacokinetics ofdigoxin ortheophylline werenot modified bytheco-administration of clopidogrel. Antacidsdid not modifytheextentofclopidogrelabsorption.

Datafromthe CAPRIE studyindicatethatphenytoin and tolbutamide which aremetabolised byCYP2C9 can be safelyco-administered withclopidogrel.

CYP2C8 substrate medicinal products: Clopidogrel has beenshownto increase repaglinide exposurein healthy volunteers.*In vitro* studieshaveshown theincreasein repaglinide exposureis due toinhibition of CYP2C8 bythe glucuronide metaboliteofclopidogrel. Dueto theriskofincreasedplasmaconcentrations, concomitant administration ofclopidogrel and drugs primarilycleared byCYP2C8 metabolism(e.g.,repaglinide, paclitaxel)should be undertaken with caution(seesection 4.4).

Apartfromthespecificmedicinalproductinteractioninformationdescribedabove, interaction studieswithclopidogrelandsomemedicinalproductscommonlyadministeredinpatients with atherothromboticdisease havenot been performed. However, patientsentered into clinical trialswithclopidogrelreceivedavarietyofconcomitantmedicinalproductsincluding diuretics,beta blockers, ACEI, calciumantagonists,cholesterolloweringagents,coronary vasodilators, antidiabeticagents(includinginsulin), antiepilepticagentsand GPIIb/IIIaantagonistswithoutevidenceofclinicallysignificantadverseinteractions.

As with other oralP2Y12 inhibitors,co-administrationofopioid agonistshasthepotentialto delayandreducetheabsorptionofclopidogrelpresumablybecauseofslowedgastric emptying.Theclinicalrelevanceisunknown.Considertheuseofaparenteralantiplateletagentinacut ecoronarysyndromepatientsrequiringco-administrationofmorphineorother opioid agonists.

Rosuvastatin: Clopidogrelhas been shown toincreaserosuvastatinexposurein patientsby2-fold(AUC) and 1.3-fold (C_{max})afteradministrationofa300mgclopidogreldose,andby1.4 fold(AUC)withouteffectonC_{max}afterrepeated administrationofa75mgclopidogreldose.

4.6 Fertility, pregnancy and lactation

Pregnancy

As no clinical data on exposure to clopidogrel duringpregnancyareavailable, it is preferablenot to use clopidogrel duringpregnancyas a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy,embryonal/foetal development, parturition or postnataldevelopment (seesection5.3).

Breast-feeding

It is unknown whetherclopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feedingshould not be continued duringtreatment with Antiplatt.

Fertility

Clopidogrel was not shown to alter fertilityin animal studies.

4.7 Effects on ability to drive and use machines

Clopidogrel has no or negligibleinfluenceon theabilityto drive and use machines.

4.8 Undesirable effects

Summaryof thesafetyprofile

Clopidogrel has been evaluated for safetyin morethan 44,000 patients who have participated in clinical studies, includingover 12,000 patients treated for 1year or more. Overall, clopidogrel 75 mg/daywas comparable to ASA 325 mg/dayin CAPRIE regardless ofage, genderand race. The clinicallyrelevant adversereactions observed in the CAPRIE,CURE, CLARITY, COMMITand ACTIVE-A studies arediscussed below.In addition to clinical studies experience, adverse reactions have been spontaneouslyreported.

Bleedingis themost common reaction reported both in clinical studies as well as in post-marketing experiencewhereit was mostlyreported duringthe first month of treatment.

In CAPRIE, in patients treated with eitherclopidogrel or ASA, the overall incidence of anybleedingwas 9.3%. Theincidenceof severe cases was similar for clopidogrel and ASA.

In CURE, there was no excess in major bleeds with clopidogrel plus ASA within 7 daysaftercoronarybypass graft surgeryin patients who stopped therapymore than five days prior to surgery.In patients who remained on therapywithin fivedays of bypassgraft surgery, theevent ratewas9.6%for clopidogrel plus ASA, and6.3% for placebo plus ASA.

In CLARITY, there wasan overall increasein bleedingin theclopidogrelplus ASA group vs. the placebo plus ASA group .Theincidence of major bleedingwas similar betweengroups . This was consistent across subgroups of patients defined bybaseline characteristics, and typeof fibrinolytic orheparin therapy.

In COMMIT, the overall rate of noncerebralmajorbleedingorcerebral bleedingwas low and similar in both groups.

InACTIVE-A, the rateofmajor bleedingwas greater in the clopidogrel +ASA group than in the placebo+ ASA group (6.7% versus4.3%). Major bleeding wasmostlyof extracranial origin in both groups(5.3% in the clopidogrel+ ASAgroup; 3.5% in the placebo +ASA group), mainlyfrom thegastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleedingin theclopidogrel + ASA treatmentgroup compared to the placebo+ ASA group (1.4% versus 0.8%, respectively). There wasno statisticallysignificant difference in the rates offatal bleeding (1.1% inthe clopidogrel + ASAgroupand 0.7% in the placebo+ASA group) and hemorrhagic stroke (0.8% and 0.6%, respectively)betweengroups.

In TARDIS, patients with recent ischemicstrokereceivingintensiveantiplatelet therapywith three medicinal products (ASA +clopidogrel+ dipyridamole)had more bleeding and

bleedingofgreaterseveritywhen compared with eitherclopidogrel alone or combined ASA and dipyridamole(adjusted common OR 2.54, 95% XCI2.05-3.16, p<0.0001).

Tabulated list of adverse reactions

Adversereactions that occurredeither during clinical studies or that were spontaneouslyreportedare presented in thetablebelow. Their frequencyis defined usingthefollowingconventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to<1/100); rare (≥1/10,000to <1/1,000); veryrare (<1/10,000), not known (cannot be estimated from the available data). Within eachsystem organ class, adversereactions are presented in order ofdecreasingseriousness.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare, not known***
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura(TTP) (see section 4.4), aplasticanaemia, pancytopenia, agranulocytosis, severe thrombocytopeni a, acquired haemophiliaA, granulocytopenia, anaemia
Cardiac disorders				Kounissyndrome (vasospastic allergic angina/ allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)(see section 4.4)*, insulin autoimmune syndrome,which can lead to severe hypoglycemia,

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
				particularlyin patients with HLA DRA4 subtype (more frequent in the Japanese population)*
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances, ageusia
Eye disorders		Eye bleeding conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratorytract bleeding (haemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Gastrointestinal hemorrhage,diarrhoea, abdominal pain,dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal hemorrhage	Gastrointestinal and retroperitoneal hemorrhagewith fatal outcome, pancreatitis, colitis (including ulceративeor lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acuteliver 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

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
				multiforme, acute generalizedexanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria,eczema, lichen planus
Reproductive systems and breast disorders			Gynaecomastia	
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	Bleedingat puncture site			Fever
Investigations		Bleedingtime prolonged, neutrophil count decreased, platelet count decreased		

*Information related to clopidogrel with frequency“not known”.

4.9 Overdose

Overdose followingclopidogrel administration maylead to prolonged bleedingtime and subsequentbleedingcomplications. Appropriatetherapyshouldbeconsideredif bleedingsareobserved.

No antidote to the pharmacological activityofclopidogrelhas beenfound.If prompt correction of prolonged bleedingtimeis required, platelet transfusion mayreverse the effects ofclopidogrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Clopidogrel is aprodrug,oneof whosemetabolites is an inhibitor of platelet aggregation. Clopidogrelmustbe metabolisedbyCYP450 enzymes to produce the active metabolite thatinhibits platelet aggregation. The active metabolite of clopidogrel selectivelyinhibits the bindingof adenosine diphosphate (ADP)to its platelet $P2Y_{12}$receptor and the subsequent ADP-mediated activation ofthe glycoprotein GPIIb/IIIa complex, therebyinhibitingplatelet aggregation. Dueto theirreversiblebinding, platelets exposed are affected for theremainderoftheir lifespan (approximately7-10 days) andrecoveryof normal platelet function occursat a rateconsistent with platelet turnover. Platelet aggregation induced byagonists other than ADP is also inhibited byblockingthe amplification of plateletactivation byreleased ADP.

Becausetheactivemetaboliteis formed byCYP450 enzymes, someofwhich are polymorphic or subject to inhibition byothermedicinal products, not all patients will have adequate platelet inhibition.

Pharmacodynamiceffects

Repeated doses of75 mg per dayproduced substantial inhibition of ADP- induced platelet aggregation from the first day; this increased progressively and reached steadystatebetween Day3 and Day7. At steadystate, the average inhibition level observed with a dose of 75 mgperdaywas between
40% and 60%. Platelet aggregation and bleedingtime graduallyreturned to baseline values,generallywithin 5 days after treatment was discontinued.

Clinical efficacy and safety

The safetyand efficacyofclopidogrel havebeenevaluated in 7 double-blind studies involvingover 100,000 patients: the CAPRIE study,a comparison of clopidogrel to ASA, andthe CURE, CLARITY, COMMIT, CHANCE, POINTand ACTIVE-Astudies comparing clopidogrel to placebo, both medicinal productsgivenin combination with ASA and other standard therapy.

Recent myocardialinfarction (MI),recentstrokeorestablishedperipheralarterial disease

The CAPRIE studyincluded 19,185 patients with atherothrombosis as manifested byrecent myocardial infarction (<35days), recent ischemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients wererandomised toclopidogrel75 mg/dayorASA325 mg/day, andwerefollowed for 1 to 3years.In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantlyreduced theincidence ofnew ischemic events (combined end point ofmyocardial infarction, ischemic strokeand vascular death) whencompared toASA.In theintention to treat analysis, 939 events were observed in theclopidogrelgroupand 1,020events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p=0.045), which corresponds,for every1,000 patients treated for 2years, to 10 [CI: 0 to 20] additional patients being preventedfrom experiencing a new ischemic event. Analysis of total

mortalityasa secondaryendpoint did not show any significant difference between clopidogrel (5.8%)and ASA (6.0%).

Ina subgroup analysis byqualifyingcondition (myocardial infarction, ischemic stroke, and PAD)the benefit appeared tobe strongest (achievingstatistical significanceatp=0.003) in patients enrolled due to PAD (especially thosewho also had ahistoryofmyocardial infarction) (RRR =23.7%; CI:8.9 to 36.2) and weaker(not significantlydifferentfrom ASA) in stroke patients (RRR =7.3%; CI: -5.7 to18.7 [p=0.258]).In patients who wereenrolled inthe trial on the sole basis of arecentmyocardial infarction, clopidogrelwas numericallyinferior, but not statisticallydifferentfrom ASA (RRR = -4.0%; CI: -22.5 to 11.7 [p=0.639]).In addition, a subgroup analysis byage suggested that the benefit ofclopidogrel in patients over 75years was less than that observed in patients ≤75years.

Since the CAPRIE trialwas not powered to evaluate efficacyof individual subgroups, it is not clearwhether the differences in relative risk reduction across qualifyingconditions are real, ora result ofchance.

Acute coronary syndrome

The CURE studyincluded 12,562 patients with non-ST segment elevation acute coronarysyndrome(unstable angina or non-Q-wave myocardial infarction) and presentingwithin 24 hoursof onset of the most recent episode of chest pain or symptoms consistentwith ischemia. Patients wererequiredto have eitherECG changescompatible with new ischemia or elevated cardiac enzymes or troponinIorT to at leasttwice the upper limit ofnormal. Patients wererandomised to clopidogrel (300 mgloadingdose followed by75 mg/day, N=6,259) or placebo(N=6,303), both given in combination with ASA (75-325 mgonce daily)and other standard therapies. Patients were treatedfor up to oneyear.In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins wereadministered in more than 90%of the patients and the relative rate of bleedingbetween clopidogrel and placebo was not significantlyaffected bythe concomitant heparin therapy.

The number of patients experiencingthe primaryendpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke]was 582 (9.3%) in the clopidogrel-treatedgroupand 719 (11.4%) in the placebo-treatedgroup, a20% relative risk reduction (95%CIof 10%-28%; p=0.00009) for the clopidogrel-treatedgroup(17% relativerisk reduction when patients were treated conservatively, 29% when theyunderwentpercutaneous transluminal coronaryangioplasty(PTCA) with orwithout stent and 10% when they underwent coronaryarterybypassgraft(CABG)).New cardiovascular events (primaryendpoint) wereprevented, 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)and14% (CI:-31.6, 44.2), duringthe 0-1, 1-3, 3-6, 6-9and 9-12 month study intervals, respectively. Thus, beyond 3 months oftreatment, the benefit observed in the clopidogrel + ASAgroup was not further increased, whereas the risk of hemorrhage persisted (see section 4.4).

Theuseof clopidogrel inCURE was associated with adecrease intheneedof thrombolytictherapy(RRR= 43.3%;CI:24.3%, 57.5%)and GPIIb/IIIa inhibitors (RRR = 18.2%;CI:6.5%, 28.3%).

Thenumberofpatientsexperiencingtheco-primaryendpoint(CVdeath, MI,stroke or refractoryischemia) was1,035 (16.5%)in the clopidogrel-treated group and 1,187 (18.8%)intheplacebo-treatedgroup,a14%relativeriskreduction(95%CIof6%-21%,p=0.0005)fortheclopidogrel-treatedgroup.Thisbenefitwasmostlydrivenby thestatisticallysignificantreductionintheincidenceofMI[287(4.6%)inthe clopidogrel treated group and 363 (5.8%)in the placebo treated group].There wasno observedeffectontherateofrehospitalisationforunstableangina.

The results obtained in populations withdifferentcharacteristics (e.g. unstable anginaor non-Q-waveMI, low to high risk levels,diabetes, needfor revascularisation, age,gender, etc.) wereconsistent with the results of the primaryanalysis.In particular, in a post-hocanalysis 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% favouringclopidogrel for theco-primaryendpoint (CV death, MI, stroke) andalso asignificant RRR of 23.9% for thesecondco-primary endpoint (CV death, MI,stroke or refractoryischemia). Moreover, the safety profile of clopidogrel in this subgroup of

patients did not raise anyparticular concern.Thus, theresults from this subset arein linewith theoverall trial results.

The benefits observed with clopidogrelwereindependent of otheracuteand long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid loweringmedicinal products, betablockers,and ACE- inhibitors). The efficacyof clopidogrel was observed independentlyof the dose of ASA (75-325 mg once daily).

In patients with acuteST-segment elevation MI, safetyandefficacyof clopidogrel have been evaluatedin 2 randomised,placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presentingwithin 12 hours of the onset of a ST elevationMIand plannedfor thrombolytictherapy. Patients received clopidogrel (300 mgloadingdose, followed by75 mg/day, n=1,752) or placebo(n=1,739), both in combination with ASA (150 to 325 mgas a loadingdose,followed by75 to 162 mg/day), afibrinolytic agent and, whenappropriate, heparin. Thepatients werefollowed for 30 days. The primary endpoint was the occurrence of thecomposite of an occluded infarct-related arteryon the predischargeangiogram, or death orrecurrent MIbefore coronaryangiography.For patients who did not undergo angiography, the primaryendpoint was death or recurrentmyocardial infarction byDay8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients ≥ 65years. 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 placebogroupreached the primaryendpoint, representinganabsolute reduction of 6.7%and a36 % odds reduction in favor of clopidogrel (95%CI:24, 47%; $p < 0.001$), mainlyrelated to a reductionin occluded infarct-related arteries. This benefit wasconsistent across all prespecified subgroups includingpatients'age and gender, infarct location, and typeof fibrinolytic or heparin used.

The 2x2 factorial designCOMMIT trial included45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MIwith supporting ECG abnormalities (i.e.ST elevation, ST depression or left bundle-branch block). Patients receivedclopidogrel (75 mg/day,n=22,961) or placebo (n=22,891), in combination with ASA (162 mg/day),for 28 days oruntil hospital discharge. Theco-primaryendpoints weredeath from anycause and the first occurrenceof re-infarction,stroke or death. The population included27.8% women, 58.4% patients≥ 60years (26%≥70years)and54.5% patients who received fibrinolytics.

Clopidogrel significantlyreduced the relative riskof death fromanycauseby7% (p=0.029),and the relative risk of the combination of re-infarction, stroke or death by9%(p=0.002), representingan absolutereduction of 0.5% and0.9%, respectively.This benefit wasconsistent across age,gender andwith or without fibrinolytics, andwas observed as earlyas24 hours.

De-escalation of $P2Y_{12}$Inhibitor Agents in AcuteCoronarySyndrome Switchingfrom a morepotent $P2Y_{12}$receptor inhibitor to clopidogrel in association with aspirin after acute phase in AcuteCoronarySyndrome (ACS) has been evaluated in two randomizedinvestigator-sponsored studies (ISS)– TOPIC and TROPICAL-ACS – with clinical outcomedata.

The clinical benefit provided bythe more potent $P2Y_{12}$inhibitors, ticagrelor and prasugrel, in their pivotal studies is related to asignificant reduction in recurrent ischemicevents(includingacute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischemic benefit was consistent throughout the firstyear,greaterreductionin ischemicrecurrenceafter ACS was observed duringtheinitial days following the treatment initiation.In contrast, *post-hoc*analyses demonstrated statisticallysignificant increases in thebleedingrisk with themorepotent $P2Y_{12}$inhibitors, occurringpredominantlyduring themaintenancephase,afterthe first month post-ACS. TOPIC and TROPICAL-ACSwere designed to studyhow to mitigatethe bleeding events whilemaintainingefficacy.

TOPIC (*Timing Of Platelet Inhibitionafter acute Coronary syndrome*) This randomized, open-label trial included ACS patients requiring percutaneous coronaryintervention (PCI). Patients on aspirin and a morepotent P2Y12blocker andwithout adverse event atone month wereassigned to switch to fixed-dose aspirin plus clopidogrel(de-escalated dualantiplatelet therapy(DAPT)) orcontinuation of their drugregimen (unchanged DAPT).

Overall, 645 of 646 patients with ST-elevation-MI(STEMI)or non-ST- elevation-MI(NSTEMI)or unstable angina wereanalyzed (de-escalated DAPT (n=322); unchanged DAPT (n=323)). Follow-up at oneyear was performedfor 316 patients (98.1%) in the de-escalated DAPTgroup and 318 patients (98.5%) in the unchanged DAPT group.The median follow-upfor both groups was 359 days. The characteristics of the studied cohort were similar in the 2 groups.

The primaryoutcome,acomposite of cardiovascular death, stroke, urgent revascularization, and BARC (BleedingAcademicResearch Consortium) bleeding≥2at 1yearpost ACS, occurred in 43 patients (13.4%) in the de- escalatedDAPTgroup and in 85 patients (26.3%)in the unchanged DAPT group($p<0.01$). This statisticallysignificant difference was mainlydriven by fewer bleedingevents, with no difference reportedin ischemic endpoints ($p=0.36$), whileBARC≥2 bleedingoccurred less frequentlyin the de- escalatedDAPTgroup (4.0%) versus 14.9%in the unchanged DAPTgroup ($p<0.01$).Bleedingevents defined asallBARC occurred in 30 patients (9.3%) in the de-escalated DAPT groupand in76 patients (23.5%) in the unchanged DAPT group($p<0.01$).

TROPICAL-ACS(*Testing Responsiveness to Platelet Inhibition on ChronicAntiplatelet Treatment for Acute Coronary Syndromes*)

This randomized, open-label trial included 2,610biomarker-positive ACS patients after successfulPCI. Patients wererandomized to receive either prasugrel 5 or 10 mg/d (Days 0-14) (n=1306), orprasugrel 5 or 10 mg/d (Days0-7) then de-escalated toclopidogrel 75 mg/d (Days8-14) (n=1304), in combination with ASA (<100 mg/day).At Day14, platelet function testing (PFT) was performed. The prasugrel-onlypatientswerecontinued on prasugrel for 11.5 months.

The de-escalated patientsunderwent high plateletreactivity(HPR) testing.IfHPR≥46 units, the patients were escalated back toprasugrel 5 or 10 mg/d for11.5 months; if HPR<46units, the patients continued on clopidogrel 75 mg/d for 11.5 months.Therefore, theguided de-escalation arm had patients on either prasugrel (40%) orclopidogrel(60%).All patients werecontinued on aspirin and were followed for oneyear.

The primaryendpoint (thecombined incidence ofCV death, MI, strokeand BARCbleeding grade≥2at 12 months) was met showingnon-inferiority. Ninety-five patients (7%)in the guided de-escalation groupand 118 patients(9%) in the controlgroup(p non-inferiority=0.0004) had an event. Theguided de-escalation did not result in an increasedcombined risk of ischemicevents (2.5% in the de-escalation group vs 3.2% in the control group; p non- inferiority=0.0115), nor in the keysecondaryendpoint of BARC bleeding≥2 ((5%) in the de-escalation group versus 6% in thecontrol group (p=0.23)).The cumulative incidence ofall bleeding events (BARCclass 1 to 5) was 9% (114 events) in theguided de-escalationgroup versus 11% (137 events) in the control group (p=0.14).

Dual Antiplatelet Therapy(DAPT) in AcuteMinorISorModerateto High-risk TIA

DAPT with combination clopidogrel and ASA asa treatment to prevent stroke afteran acuteminorISormoderate tohigh-risk TIAhas been evaluated intwo randomized investigator-sponsored studies (ISS) –CHANCE and POINT – with clinical safetyandefficacyoutcome data.

CHANCE(*Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events*)

This randomized, double-blinded, multicenter,placebo-controlled clinical trial included 5,170 Chinese patients with acute TIA(ABCD2 score≥4) oracute minor stroke (NIHSS ≤3). Patients in both groupsreceived open-label ASAon day1(with the dose rangingfrom 75 to 300 mg, at the discretion of thetreatingphysician). Patients randomlyassigned tothe clopidogrel–ASAgroup received a loadingdose of300 mgofclopidogrelon day1,followed bya dose of 75

mgofclopidogrelper dayon days 2 through 90, and ASA at a doseof 75 mgper dayon days 2 through 21. Patients randomlyassigned to the ASAgroupreceived a placeboversion of clopidogrelon days 1 through 90andASAat a dose of 75 mgper dayon days 2 through 90.

The primaryefficacyoutcome was anynew strokeevent (ischemic and hemorrhagic) in the first90 daysafteracute minorISor high-risk TIA. This occurred in 212 patients (8.2%) in the clopidogrel-ASA groupcompared with303 patients (11.7%) in the ASA group (hazard ratio [HR], 0.68; 95% confidenceinterval [CI],0.57 to 0.81; P<0.001).ISoccurred in 204 patients (7.9%) in the clopidogrel–ASA groupcomparedwith 295 (11.4%) in theASA group(HR, 0.67; 95% CI, 0.56 to 0.81; P<0.001). Hemorrhagicstroke occurred in 8 patients in each of the two studygroups (0.3% of eachgroup). Moderate or severehemorrhage occurred in sevenpatients (0.3%) in the clopidogrel–ASAgroupand in eight (0.3%) in theASA group(P = 0.73). The rate ofanybleedingevent was 2.3% in the clopidogrel–ASAgroup as compared with 1.6% in the ASA group (HR, 1.41; 95% CI, 0.95 to 2.10; P =0.09).

POINT(*Platelet-Oriented Inhibition in New TIAand Minor Ischemic Stroke*) This randomized, double-blinded, multicenter,placebo-controlled clinical trial included 4,881 international patients with acute TIA (ABCD2 score≥4)or minor stroke (NIHSS ≤3). All patients in both groups received open-labelASA on day1 to 90(50-325 mgdependingupon the discretion of the treating physician). Patients randomlyassigned to the clopidogrelgroup receivedaloadingdose of600 mgofclopidogrel on day1, followed by75 mgof clopidogrel per dayon days2 through 90. Patientsrandomlyassigned to the placebogroupreceived clopidogrel placebo on days1 through 90.

Theprimaryefficacyoutcomewas acompositeof major ischemic events (IS, MIordeath from an ischemic vascularevent)at day90. This occurred in 121 patients (5.0%) receiving clopidogrel plus ASA compared with 160 patients (6.5%) receivingASA alone (HR, 0.75; 95% CI,0.59 to 0.95; P= 0.02). The secondaryoutcome ofISoccurred in112 patients (4.6%) receivingclopidogrel plus ASA compared with155 patients(6.3%) receivingASA alone(HR, 0.72;95% CI, 0.56 to 0.92; P= 0.01). The primarysafetyoutcome of major hemorrhage occurred in23 of 2,432 patients (0.9%) receivingclopidogrelplus ASA and in 10 of

2,449patients (0.4%) receiving ASA alone (HR, 2.32; 95% CI, 1.10 to 4.87; P = 0.02). Minor hemorrhage occurred in 40 patients (1.6%) receivingclopidogrel plus ASA and in13 (0.5%) receivingASA alone(HR,3.12; 95% CI, 1.67 to 5.83; P = 0.001).

CHANCE and POINT Time Course Analysis

Therewas no efficacybenefit of continuing DAPT beyond21 days. A time- course distribution of major ischemicevents andmajor hemorrhages by treatment assignment was done to analyze the impact of the short-term time- course ofDAPT.

Table 1- Time coursedistributionofmajor ischemic events andmajor hemorrhages by treatment assignmentinCHANCE andPOINT

Outcomes in CHANCE and POINT		No. of events			
	Treatment assignment	Total	1st week	2nd week	3rd week
Majorischemic events	ASA(n=5,035)	458	330	36	21
	CLP+ASA(n=5,016)	328	217	30	14
	Difference	130	113	6	7
Major Hemorrhage	ASA(n=5,035)	18	4	2	1
	CLP+ASA(n=5,016)	30	10	4	2
	Difference	-12	-6	-2	-1

Atrial fibrillation

The ACTIVE-Wand ACTIVE-A studies, separatetrials in the ACTIVE program, included patients with atrial fibrillation (AF)who had at least one risk factor for vascularevents. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if theywerecandidates for vitamin K antagonist (VKA) therapy(such as warfarin). TheACTIVE-A studyincluded patients who could not receive VKA therapybecause theywereunable or unwillingto receivethetreatment.

TheACTIVE-W studydemonstrated that anticoagulant treatment with vitaminK antagonists was moreeffective than with clopidogrel and ASA.

The ACTIVE-A study(N=7,554) was a multicenter, randomized, double-blind, placebo-controlled studywhichcompared clopidogrel75 mg/day+ASA (N=3,772) to placebo +ASA (N=3,782). The recommended dose for ASA was 75 to 100mg/day.Patients were treated for up to 5years.

Patients randomized in theACTIVE program were thosepresentingwith documented AF, i.e., eitherpermanent AFor at least 2 episodes of intermittent AFin the past 6 months, and had at least one of the following risk factors:age≥75years orage55 to 74years andeitherdiabetesmellitus requiringdrug therapy, or documented previous MIordocumented coronaryarterydisease; treated for systemichypertension; prior stroke, transient ischemic attack (TIA), ornon-CNS systemic embolus; left ventricular dysfunction with leftventricularejection fraction <45%; or documentedperipheral vasculardisease. The mean $CHADS_2$score was 2.0 (range0-6).

Themajor exclusion criteriafor patients weredocumented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count < 50 $x10^9$/l); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance toanyof the two compounds.

Seventy-three percent (73%) of patients enrolled into theACTIVE-A study wereunableto takeVKAdueto physicianassessment, inabilityto comply withINR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk ofbleeding; for 26% of the patients, the physician's decision wasbased on thepatient's unwillingness to takeVKA.

The patient population included 41.8 % women. The mean age was 71years,41.6% of patients were ≥75years. 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 primaryendpoint (time to first occurrenceof stroke, MI,non-CNS systemic embolism or vascular death)was832 (22.1%) in thegrouptreated with

clopidogrel + ASA and 924 (24.4%)in the placebo+ ASAgroup(relative riskreduction of11.1%; 95% CIof 2.4%to19.1%; p=0.013), primarilydue to a largereduction in the incidence of strokes. Strokes occurredin 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receivingplacebo +ASA (relativerisk reduction,28.4%; 95% CI, 16.8% to 38.3%; p=0.00001).

Paediatric population

Ina dose escalation studyof 86 neonates orinfants up to 24 months of ageat risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kgin neonates and infants and 0.15 mg/kgonlyin neonates. The dose of 0.2mg/kgachieved the mean percent inhibition of49.3% (5 µMADP-induced platelet aggregation)which was comparable to that of adults takingAntiplatt75 mg/day.

Ina randomised, double-blind, parallel-group study(CLARINET), 906 paediatricpatients (neonates and infants)with cyanoticcongenital heart Dear IRA team, Please confirm this with F & D disease palliated with a systemic-to-pulmonaryarterial shunt wererandomised to receiveclopidogrel 0.2mg/kg(n=467) or placebo (n=439) alongwith concomitant backgroundtherapyup to the time ofsecond stage surgery. The mean time between shunt palliation and first administration of studymedicinal product was 20 days.Approximately88% of patients receivedconcomitant ASA (range of1 to 23 mg/kg/day). Therewas nosignificant difference betweengroups in the primarycompositeendpointof death, shunt thrombosis or cardiac-related intervention prior to 120 days ofage followingan event considered of thrombotic nature (89 [19.1%]for the clopidogrelgroupand90 [20.5%]for the placebogroup) (seesection 4.2).Bleedingwas the most frequentlyreportedadverse reaction inboth clopidogrel and placebogroups; however, there was no significant difference in the bleedingratebetween groups.In the long-termsafetyfollow-upofthis study, 26 patients with the shunt still in place at oneyearofage received clopidogrel up to 18 monthsof age. No new safetyconcerns were noted duringthis long-term follow-up.

TheCLARINET and thePICOLO trials wereconducted using a constituted solution of clopidogrel.In arelativebioavailabilitystudyin adults, the constituted solution of clopidogrel

showed asimilar extent and slightlyhigher rateofabsorption of themain circulating(inactive)metabolite compared to the authorised tablet.

5.2 Pharmacokinetic properties

Absorption

After single andrepeatedoral doses of75 mgperday,clopidogrel is rapidly absorbed. Mean peak plasma levelsof unchangedclopidogrel (approximately
2.2-2.5 ng/ml after a single 75 mgoral dose) occurred approximately
45 minutes after dosing.Absorption is atleast 50%, based on urinaryexcretion of clopidogrel metabolites.

Distribution

Clopidogrel and themain circulating(inactive) metabolitebind reversibly*in vitro* to human plasma proteins (98% and 94%respectively).The bindingis non-saturable*in vitro* over a wideconcentration range.

Biotransformation

Clopidogrel is extensivelymetabolisedbytheliver.*In vitro* and *in vivo*, clopidogrel is metabolised accordingto two mainmetabolicpathways: one mediated byesterasesand leadingto hydrolysis into its inactive carboxylicacid derivative(85% ofcirculatingmetabolites), and onemediated bymultiplecytochromes P450. Clopidogrel is firstmetabolised to a 2-oxo-clopidogrel intermediatemetabolite.Subsequent metabolism of the2-oxo-clopidogrel intermediatemetaboliteresults in formation of the activemetabolite, athiol derivativeofclopidogrel.The activemetaboliteis formed mostlybyCYP2C19 with contributions from several other CYP enzymes, includingCYP1A2, CYP2B6 and CYP3A4. The activethiol metabolite which has been isolated*in vitro*, binds rapidlyand irreversiblyto platelet receptors, thus inhibiting platelet aggregation.

The $C_{max}$of the active metabolite is twice as highfollowinga single 300 mg clopidogrel loadingdoseas it is after four days of75 mgmaintenance dose. C_{max}occurs approximately30 to 60 minutes afterdosing.

Elimination

Following an oral dose of ^{14}C-labelled clopidogrelin man, approximately50% was excreted in the urineand approximately46%in the faeces in the 120-hour interval after dosing.After asingle oral dose of 75 mg, clopidogrelhas ahalf-life ofapproximately6 hours. The elimination half-life of the main circulating(inactive)metabolite was 8 hours aftersingle andrepeated administration.

Pharmacogenetics

CYP2C19 is involved inthe formationof both the active metabolite and the 2- oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokineticsand antiplatelet effects, as measured by*exvivo* platelet aggregation assays, differ accordingto CYP2C19 genotype.

The CYP2C19*1 allele corresponds to fullyfunctional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majorityofreduced function alleles in Caucasian (85%) andAsian (99%) poor metabolisers. Otheralleles 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 allelesas defined above. Published frequencies for the poor CYP2C19 metabolisergenotypes areapproximately2%for Caucasians, 4% for Blacks and 14% forChinese. Tests areavailable to determine a patient’s CYP2C19 genotype.

A crossover studyin 40healthysubjects, 10 eachin the four CYP2C19 metabolisergroups (ultrarapid, extensive, intermediate and poor),evaluated pharmacokineticand antiplatelet responses using 300 mgfollowed by75 mg/dayand 600 mgfollowed by150 mg/day,each for a total of 5 days (steadystate).No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) wereobserved between ultrarapid, extensive

andintermediatemetabolisers.In poor metabolisers, activemetabolite exposurewas decreased by63-71% compared to extensive metabolisers. After the 300 mg/75 mgdose regimen, antiplatelet responses weredecreased in thepoor metabolisers with meanIPA (5μM ADP) of24% (24 hours) and 37% (Day5) as compared toIPA of39% (24 hours)and 58% (Day5) in theextensive metabolisersand 37% (24 hours) and 60%(Day5)inthe intermediate metabolisers. When poor metabolisers received the600 mg/150 mg regimen,active metabolite exposure wasgreater than with the300 mg/75 mg regimen.In addition,IPA was 32%(24 hours) and 61% (Day5), which weregreater than in the poor metabolisers receivingthe300 mg/75 mg regimen,and weresimilar to the other CYP2C19 metabolisergroupsreceivingthe 300mg/75 mg regimen. Anappropriate doseregimenfor this patient population has not been established inclinical outcome trials.

Consistent with the above results, in ameta-analysis including6 studies of335 clopidogrel-treated subjects at steadystate, it wasshown that activemetabolite exposure was decreased by28%for intermediatemetabolisers, and 72% for poor metabolisers whileplateletaggregation inhibition (5μM ADP) was decreased with differences inIPA of5.9% and 21.4%, respectively,when compared to extensivemetabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrelhas not been evaluatedin prospective, randomised, controlled trials. There have been anumber of retrospectiveanalyses, however, to evaluatethis effect in patients treated with clopidogrelfor whom there are genotypingresults: CURE (n=2721), CHARISMA (n=2428),CLARITY-TIMI28(n=227), TRITON-TIMI38 (n=1477), and ACTIVE-A (n=601), aswell as a numberof published cohortstudies.

In TRITON-TIMI38 and3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poormetaboliser status had a higherrate ofcardiovascularevents (death,myocardial infarction, and stroke) or stent thrombosis compared to extensivemetabolisers.

In CHARISMAand onecohort study(Simon), an increased event rate was observed onlyin poor metabolisers whencompared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of thecohort studies (Trenk), no increased event ratewasobserved based on metaboliser status.

None of theseanalyses were adequatelysized to detect differences in outcome in poor metabolisers.

Special populations

The pharmacokinetics ofthe active metabolite ofclopidogrel is not known in these special populations.

Renal impairment

After repeated doses of 75 mgclopidogrelper dayin subjects with severe renal disease(creatinine clearancefrom 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation waslower (25%) than that observed in healthysubjects, however, theprolongation of bleedingtimewas similar to that seen in healthy subjects receiving75 mg of clopidogrel per day.Inaddition, clinical tolerance wasgood in all patients.

Hepaticimpairment

After repeated doses of 75 mgclopidogrelper dayfor 10 days in patients with severe hepatic impairment, inhibition ofADP-induced platelet aggregation was similar to that observed in healthysubjects. Themean bleedingtime prolongation was also similar in the two groups.

Race

Theprevalenceof CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differsaccordingtorace/ethnicity(see Pharmacogenetics). From literature, limited datain Asian populations are availableto assess theclinical implication of genotypingof this CYP on clinical outcomeevents.

5.3 Preclinical safety data

Duringnon-clinical studies in ratand baboon, themost frequentlyobserved effects wereliver changes. These occurredat doses representing at least 25 times the exposureseen in humans receivingtheclinical doseof 75 mg/day and werea consequenceof an effect on hepatic metabolisingenzymes. No effect on hepaticmetabolisingenzymeswas observed in humans receiving clopidogrel at the therapeuticdose.

At veryhigh doses, apoor gastrictolerability(gastritis, gastricerosions and/or vomiting)of clopidogrelwas also reported in rat and baboon.

There was no evidence ofcarcinogeniceffect when clopidogrel was administered for 78 weeks to mice and 104 weeksto rats whengiven at doses up to 77 mg/kgper day(representingat least 25 times the exposureseen in humans receivingtheclinical dose of 75 mg/day).

Clopidogrel has been tested in a range of*in vitro*and *in vivo*genotoxicity studies, and showed nogenotoxic activity.

Clopidogrel wasfound to have no effect on the fertilityof male and femalerats and was not teratogenic in eitherrats orrabbits. When given to lactatingrats, clopidogrel caused a slight delayin thedevelopment of the offspring. Specific pharmacokinetic studiesperformedwithradiolabelledclopidogrel have shown that the parent compoundor its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), oran indirect effect (low palatability)cannot beexcluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide (Colloidal Anhydrous Silica)

Crospovidone
Lactose (Directly compressible)
Starch (Maize)
Sodium Stearyl Fumarate
Talc
Instamoist Shield -A21D00098
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not Known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu-Alu Blister Pack.

6.6 Special precautions for disposal

Anyunused medicinal product or waste material should be disposed of in accordancewith local requirements.

7. MARKETING AUTHORISATION HOLDER

TROIKAA PHARMACEUTICALS LTD.
Troikaa House, Commerce House-1,
Satya Marg,Bodakdev,
Ahmedabad - 380 054,
Gujarat, India.
Phone : +91-79- 26856242/43/44/45,
Fax : +91-79-26856246
E-mail:regaffairs@troikaapharma.com

Manufacturing Site:
TROIKAA PHARMACEUTICALS LTD.
C-1, Sara Industrial Estate, Selaqui,
Dehradun-248197, Uttarakhand, India.
Telephone: +91-135-2699146, 2698819
Fax: +91-135-2698059
www.troikaa.com
Email: regaffairs@troikaapharma.com

8. MARKETING AUTHORISATION NUMBER(S)

TRO/IND/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- Date of first authorization : 07-Sep-2012
- Date of renewal : 28-Mar-2017

10. DATE OF REVISION OF THE TEXT

23/08/2023