



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Clopidogrel / Acetylsalicylic acid Teva

International non-proprietary name: clopidogrel / acetylsalicylic acid

Procedure No. EMEA/H/C/002272/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

AA	Arachidonic acid
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event
Al(u)	Aluminium
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
AUC	Area under the curve
b.i.d.	Twice daily (bis in die)
BCS	Biopharmaceutics Classification System
BMI	Body-mass index
BMS	Bare-metal stent
BP	British Pharmacopoeia
BT	Bleeding time
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event
CEP	certificate of suitability
CFR	Cyclic flow reduction
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic
CI	Confidence interval
CKD	Chronic kidney disease
Cr	Creatinine Clearance
C _{max}	Maximum plasma concentration
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COX	Cyclooxygenase
CREDO	Clopidogrel for the Reduction of Events During Observation
CRS	chemical reference standard
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischaemic Events
CV	Cardiovascular
CYP 450	Cytochrome P 450
DAD	diode array detection
DES	Drug-eluting stent
DNA	Deoxyribonucleic acid
ED ₅₀	The half -maximal effective dose
EEG	Electroencephalography
F	Fasted animals
FCC	Food Chemicals Codex
GC	Gas chromatography
GCL	Gas liquid chromatograph
GI	Gastrointestinal
GP	Glycoprotein
GPL	Good laboratory practise
HCE	Human carboxylesterase
HDPE	High density polyethylene
HPLC	High-performance liquid chromatography
HR	Hazard ratio

hsCRP High-sensitivity C-reactive protein
IC50 The dose needed to reduce platelet aggregation by 50%
ICAM Intercellular adhesion molecule
ICH I Intracerebral hemorrhage Infarction
IPC In-process controls
IQR Interquartile range
IR Infrared spectroscopy
KF Karl-Fischer
KS Dissociation constant
LD50 Lethal dose in 50% of animals
LDL Low density lipoprotein
LDPE Low density polyethylene
LO Lipoxigenase
LoD Limit of detection
LOD Loss on drying
LoQ Limit of quantitation
MACE Major adverse cardiovascular events
MCP Monocyte chemotactic protein
MES Microembolic signals
MI Myocardial infarction
MMP Matrix metalloproteinase
mRNA Messenger ribonucleic acid
NACE Net adverse clinical events
NF Nonfasted animals
NF National Formulary
NIR Near infrared spectroscopy
NLT Not lower than
NMR Nuclear magnetic resonance
NNT Number needed to treat
NO Nitric oxide
NOEL No observed effect level
NSAID Non-steroidal anti-inflammatory drug
NSTEMI Non-ST-segment elevation myocardial infarction
NZW New Zealand White
o.d. Once daily
OPA Oriented polyamide
OR Odds ratio
PAD Peripheral arterial disease
PC Phosphatidylcholine
PCI Percutaneous coronary intervention
PE Polyethylene
PEG Polyethylene glycol
PET Polyethylene terephthalate
PG Prostaglandin
PGG₂, PGH₂ Prostaglandin endoperoxide
PGI₂ Prostacyclin
PGI₂ Prostacyclin
P-gp P-glycoprotein
Ph. Eur. European Pharmacopoeia
PI3K Phosphoinositol 3-kinase
PKA Protein kinase activity
PIA Platelet antigen
PON1 Paraoxonase-1

PP Polypropylene
PPI Proton pump inhibitor
ppm Parts per million
PS Phosphatidylserine
PVC polyvinyl chloride
RH Relative humidity
ROS Reactive oxygen species
RPA Residual platelet aggregation
rpm Rotations per minute
RR Relative Risk
RRR Relative risk Reduction
RT Room temperature
sCD40L Soluble cluster of differentiation 40 ligand
SDS sodium dodecyl sulfate
SP Sphingomyelin
Stabilization, Management, and Avoidance
t_{1/2} Half-life
TAMC Total aerobic microbial count
TD50 Median toxic dose
TDI Tolerable daily intake
TEG Thrombelastography
TF Tossie factpr
TIA Transient ischemic attack
T_{max} Time to maximum plasma concentration
TNF- α Tumor necrosis factor α
TRAP Thrombin receptor agonist peptide
TRITON–TIMI 38 Trial to Assess Improvement in Therapeutic Outcomes by Optimizing
TTP Thrombotic thrombocytopenic purpura
TX Thromboxane
TxA₂ Thromboxane A₂
TYMC Total yeasts/moulds count
UA Unstable Angina
USP United States Pharmacopoeia
UV ultraviolet
VASP Vasodilator-stimulated phosphoprotein
VCAM Vascular adhesion molecule
XRPD X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 3 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Clopidogrel / Acetylsalicylic acid Teva, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2009. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication :

Clopidogrel/Acetylsalicylic acid Teva is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Fixed-dose combination medicinal product for continuation of therapy in:

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

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P /270/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

Manufacturer(s) responsible for batch release

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

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

Teva Sante
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Sens, 89107
France

Teva UK limited
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BN22 9AG, United Kingdom

Teva Operations Poland Sp. z o.o.
Sienkiewicza Str. 25
99-300 Kutno
Poland

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

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

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

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP` :

Rapporteur: Bart Van der Schueren

Co-Rapporteur: Alar Irs

- The application was received by the EMA on 3 December 2012.
- The procedure started on 21 August 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 November 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 November 2013.

- During the meeting on 18 December 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 19 December 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 February 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the consolidated List of Questions to all CHMP members on 31 March 2014.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 10 April 2014.
- During the CHMP meeting on 25 April 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2014.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 12 June 2014.
- During the meeting on 26 June 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Clopidogrel / Acetylsalicylic acid Teva.

2. Scientific discussion

2.1. Quality aspects

2.1.1. Introduction

The finished product is presented as film-coated tablets containing 75 mg/75 mg and 75 mg/100 mg of clopidogrel and acetylsalicylic acid as active substances respectively.

Other ingredients are:

Tablet core:

Lactose monohydrate
 Microcrystalline cellulose
 Hydroxypropyl cellulose
 Crospovidone
 Stearic Acid
 Croscarmellose sodium
 Hydrogenated vegetable oil
 Sodium lauryl sulfate

Tablet coating:

75 mg/75 mg
 Hypromellose 15 cP
 Polydextrose
 Titanium dioxide (E171)
 Quinoline yellow aluminium lake (E104)
 Talc
 Maltodextrin
 Medium chain triglycerides
 Iron oxide yellow (E172)

75 mg/100 mg
Hypromellose 15 cP
Polydextrose
Titanium dioxide (E171)
Talc
Maltodextrin
Medium chain triglycerides
Iron oxide yellow (E172)
Carmine (E120)
Iron oxide red (E172)

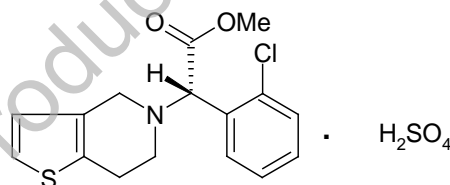
The product is available in Al/Al blisters with desiccant, white HDPE bottles with PP child-resistant closure and desiccant and white HDPE multilayer bottles with PP child-resistant closure and desiccant as described in section 6.5 of the SmPC.

2.1.1. Active Substance

General information

Clopidogrel hydrogen sulfate

The chemical name of clopidogrel hydrogen sulfate is thieno [3,2-c] pyridine-5(4H)-acetic acid, alpha-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S) -, sulphate (1:1) . Clopidogrel hydrogen sulfate has the following structure:



Clopidogrel hydrogen sulphate is a white to off-white powder, non-hygroscopic, which melts at ± 177 °C. It is freely soluble in water and methanol, practically insoluble in ether. The octanol / water partition coefficient at pH 7.4 is about 3.9, its pKa is about 4.55. It is a chiral substance due to presence of one chiral centre. Three positional isomers and one optical isomer exist. The substance used in the manufacture of Clopidogrel / Acetylsalicylic acid Teva is the (S) enantiomer.

Two polymorphic forms (form I and II) of clopidogrel hydrogen sulphate are known. The substance used in the manufacture of the drug product is clopidogrel hydrogen sulphate form II which is thermodynamically more stable than form I.

As there is a monograph of clopidogrel hydrogen sulphate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The manufacturer of clopidogrel hydrogen sulphate obtained a Certificate of suitability with requirements of European Pharmacopoeia (CEP). The detailed information on characterisation and control of the substance, reference materials and container closure system was provided to the EDQM and assessed before granting the CEP.

Specification

The active substance specification includes tests for description (visual), identity (IR, HPLC), identification of sulfate (Ph. Eur.), polymorphism (XRPD), heavy metals (Ph. Eur.), water content (KF), sulphated ash (Ph. Eur.), appearance of solution (clarity and colour (Ph. Eur.)), enantiomeric purity (HPLC), related substances (HPLC), assay by titration (Ph. Eur.), residual solvents (GC), particle size distribution (laser diffraction), bulk density (In-house) and tapped density(In-house).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on four batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents (GC). All additional methods have been adequately validated and described according to ICH Q2.

Stability

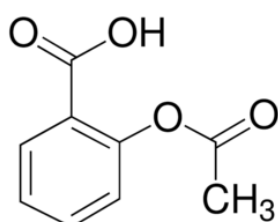
Stability data on 8 production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions at 2-8 °C and under accelerated conditions at 25 °C / 60% RH for up to six months according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Acetyl salicylic acid

The chemical name of acetyl salicylic acid is 2-acetoxybenzoic acid and it has the following structure:



It is a white crystalline powder with melting point at 156 - 161 °C, freely soluble in alcohol, soluble in chloroform, ethyl acetate and ether and slightly soluble in water. Its octanol / water partition coefficient is 13.49 and its pKa is 3.5.

As there is a monograph of acetyl salicylic acid in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The manufacturer of acetylsalicylic acid obtained a Certificate of suitability with requirements of European Pharmacopoeia (CEP). The detailed information on characterisation and control of the substance, reference materials and container closure system was provided to the EDQM and assessed before granting the CEP.

Specification

The active substance specification includes tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identity (Ph. Eur.), identification (Ph. Eur.), appearance of solution (Ph. Eur.), related substances (Ph. Eur.), heavy metals (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Ph. Eur.) and particle size (vibrating sieves).

The analytical methods used have been adequately described.

Batch analysis data on a number of batches of the active substance are provided. The results are within the specification and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Stability

A retest period and storing conditions of the drug substance are confirmed in the CEP.

2.1.2. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the development was to formulate an immediate-release tablet containing qualitatively and quantitatively the same drug substance as the mono products that already exist in the market.

The active ingredients are combined from two separate granulates that are mixed together to form a monolithic tablet. In both tablet strengths, the percentage of clopidogrel hydrogen sulphate granulate is the same, while the percentage of the acetylsalicylic granulate is proportional to the strength.

The choice of the formulation and manufacturing process is based on the manufacturer's experience with the mono-product clopidogrel hydrogen sulphate tablets and products containing acetylsalicylic acid. A

wet granulation process with ethanol was selected for clopidogrel hydrogen sulphate while dry granulation was selected for acetylsalicylic acid.

The physicochemical properties of the drug substance relevant for the drug product performance include polymorphism, solubility and impurity profile of the active substances. The polymorphic form of clopidogrel hydrogen sulphate is not susceptible to change upon storage of the drug substance itself and during the manufacture of the tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is Al/Al blisters with desiccant, white HDPE bottles with PP child-resistant closure and desiccant and white HDPE multilayer bottles with PP child-resistant closure and desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of wet granulation of the clopidogrel hydrogen sulphate granulate, dry granulation of acetylsalicylic acid granulate, followed by final blending of both granulates and compression in one tablet. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for manufacture of immediate release tablets.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and these include description (visual), identification (HPLC-DAD), dissolution (Ph. Eur., HPLC), assay (HPLC), related substances (HPLC), uniformity of dosage units (HPLC), water content (KF), microbial quality (Ph. Eur.) and colour identification.

Batch analysis results are provided for four pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on for four pilot scale batches of finished product stored under long term conditions for 18 months at 25 °C / 60% RH and for up to 12 months at intermediate conditions at 30 °C / 65% RH according to the ICH guidelines were provided. Open container studies were also carried out at 25 °C / 60% RH for 30 and 60 days. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, dissolution, related substances, water content and microbial quality. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results show that Clopidogrel/Acetylsalicylic acid Teva are sensitive to light.

Stability studies indicated that a desiccant is required in the primary packaging. Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose used in the manufacture of Clopidogrel/Acetylsalicylic acid Teva is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.1.3. Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.1.5. Recommendation(s) for future quality development

NA

2.2. Non-clinical aspects

The non-clinical data are based on literature review of published studies in animals and in vitro models. The pharmacological and toxicological features of Clopidogrel/Acetylsalicylic acid Teva are well known. Moreover, both compounds have been extensively used in humans in monotherapy as well as in combination.

2.2.1. Pharmacology

Primary pharmacodynamics

Clopidogrel

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

The mechanism of the antiplatelet action of clopidogrel is mediated through a metabolite, the structure of which has been identified during the process of regulatory assessment of the marketing authorization application of the Plavix file. This metabolite has been isolated and its structure characterized as a thiol derivative of 2 oxo clopidogrel. In vitro, in the absence of hepatic biotransformation no effect on platelet aggregation by clopidogrel could be observed, demonstrating the metabolite associated effect. The pharmacological target of this active metabolite is a Gi2 coupled receptor designated as P2Y12. The molecular interaction between the clopidogrel active metabolite and the P2Y12 receptor consists in the formation of a disulfur bridge between the reactive thiol of the molecule and cysteine 97 of P2Y12, causing the disruption of receptor complexes and translocation from platelet membrane microdomains. The activity of clopidogrel on platelet aggregation was appropriately evaluated in vitro and ex vivo.

Acetylsalicylic acid (ASA)

ASA inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A₂, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet. The pharmacological profile of ASA as a cyclooxygenase (COX) inhibitor (both COX-1 and COX-2) has been extensively established. It is active in most conventional models of inflammation, irrespective of their different mechanisms. ASA has also been shown to be a peripheral analgesic and antipyretic. The anti-thrombotic activity of ASA is based on a specific anti-platelet activity due to selective acetylation of thrombocyte COX-1 and on a fibrinolytic activity due to N-acetylation of fibrinogen.

Clopidogrel/ASA combination

The synergistic over potentiation obtained when ASA and clopidogrel are given in combination has been demonstrated in some studies. The observed additive effect strongly suggests that the combined inhibition of 1/ COX (and subsequently of thromboxane synthesis) by ASA and 2/ ADP receptors by clopidogrel can provide substantial protection against platelet aggregation and thrombosis at the site of endothelial injury, in humans.

Secondary pharmacodynamics

Secondary pharmacodynamic studies with the combination were not performed and are not requested in view of the extensive data available on the use of combined individual medicinal products at the dosage now being applied for in the Clopidogrel/ASA application.

Safety pharmacology

Safety pharmacology studies with clopidogrel did not reveal any relevant effect to the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems.

The targets for toxicity of acetylsalicylic acid have been identified in nonclinical studies and clinical experience has put these findings into context.

Additional safety pharmacology studies in animals with the combination were not performed and are not required given the extensive clinical data available on the combined use of individual medicinal products at the dosage being applied for the combination.

Pharmacodynamic drug interactions

In summary, no preclinical pharmacology studies were conducted with the Clopidogrel/ASA formulation. The pharmacological features of Clopidogrel/ASA have been extensively studied. As there is no evidence to suggest a possible negative interaction between clopidogrel and ASA, this is considered acceptable.

2.2.2. Pharmacokinetics

Clopidogrel

The metabolism and disposition of clopidogrel were evaluated in several in vitro and in vivo studies performed in the mouse, rat, rabbit and baboons. The pharmacokinetics of ASA has been investigated in the rat (with some further limited data in the dog and monkey) and is largely documented in humans.

Clopidogrel is well absorbed (at least 50%), and undergoes extensive metabolism. Twenty metabolites were identified. In all species, the primary biotransformation pathways consist of: hydrolysis of the ester function by carboxylesterases (leading to the formation of SR26334, the main circulating metabolite); sulfoxidation, oxidation of the tetrahydropyridine moiety, and glucuronidation of SR26334. The main metabolite found in plasma, the carboxylic acid derivative (SR26334), is inactive. The peak plasma concentration of SR26334 was observed 1 to 2 hours after oral administration of clopidogrel in all the studied animal species. The active thiol metabolite of clopidogrel isolated following incubation of clopidogrel with hepatic microsomal fractions has not been detected in plasma.

The binding of clopidogrel and SR26334 to plasma proteins was high (98% and 94% respectively) in all species and distributed widely in tissues. Radioactivity was slowly eliminated from the tissues, and in particular from arterial wall, thyroid gland, cartilage, skin and spleen. Transfer of the radioactivity to the developing foetus was observed in pregnant rats and rabbits. The majority of radioactivity was excreted within 48 hours in all species. In lactating rats, clopidogrel and/or its metabolites levels in milk were 0.5 to 2.6 times higher than the maternal plasma levels.

ASA

After oral administration, ASA is rapidly absorbed to give appreciable concentrations in plasma even after 30 minutes before a gradual decline with conversion of ASA to salicylate. Both ASA and salicylate are rapidly and extensively distributed in body fluids (including breast milk). They are localized in excretory organs (liver and kidney) and glandular stomach and cross the placental barrier. ASA binds strongly to plasma proteins and may displace certain compounds including other acidic nonsteroidal anti-inflammatory drugs (NSAID) or coumarins. The biotransformation of ASA proceeds in two steps. The first step is independent of dose and involves conversion to salicylate by pre-absorptive hydrolysis in the gut mucosa and a hepatic first-pass effect. The second step, the metabolic conversion of salicylate and subsequent formation of conjugates and their renal excretion, is dose-dependent. Salicylic acid is the main and rate-limiting metabolite in humans.

Clopidogrel/ASA combination

The PK of combined Clopidogrel/ASA has not been addressed in dedicated studies. Based on the pharmacokinetic characteristics of clopidogrel and ASA and on the drug-drug interaction profiles of each of these drugs, no pharmacokinetic interactions between the 2 compounds are expected.

Both compounds are highly protein bound and undergo hepatic metabolism. Although these aspects might raise the possibility for pharmacokinetic interaction, this is expected to have been covered in the

clinical use, since the combined use of both compounds has been taking place already. Therefore, it is considered that there is no need for dedicated pharmacokinetic and interaction studies with the fixed dose combination.

2.2.3. Toxicology

Single -dose toxicity

Clopidogrel

The oral LD50 for Clopidogrel in rats is 620 (males; 2420 mg/kg) and 490 (females; 1910 mg/kg) times the daily recommended therapeutic dose in humans. The intravenous LD50 was 22 (males) and 17 (females) times lower. Similar results were obtained in mice.

ASA

The oral LD50 of ASA was 960 mg/kg for mice, 1430-1600 mg/kg for rats and 1075-1095 mg/kg for Guinea pig, around and about 100 to 200 times the daily recommended therapeutic dose in humans.

In conclusions, oral single dose toxicity of both Clopidogrel and ASA is low.

Repeat -dose toxicity

Clopidogrel

At repeated doses of 400 mg/kg/day Clopidogrel and higher, increased liver weight, associated with hypertrophy of the smooth endoplasmic reticulum in centrolobular hepatocytes induced by an effect on hepatic enzymes, was observed. This was reflected in elevated plasma cholesterol levels. Based on liver weight, the NOEL was 27 mg/kg/day (rats) and 65 mg/kg/day (baboons), corresponding to an exposure of 7 times (rats) and more than 10 times (baboons) the recommended therapeutic dose in humans.

ASA

Repeat dose toxicity of ASA in rats with 200 mg/kg but not 50 mg/kg revealed increased liver weight without histopathological lesions. No morbidity associated with gastric erosions and ulceration was detected. Nephrotoxicity (papillary necrosis, decrease in urinary concentration) could be induced after 40-83 weeks of treatment with 120-230 mg/kg/day.

In mice, doses of 130-1270 mg/kg/day induced an overall severe deterioration of general condition, including hair loss, decreased litter size and a highly significantly shortening of survival time.

ASA is stated to play a role in the Reye's syndrome; therefore, ASA should not be given to children younger than 12 years old.

Epithelial desquamation, hyperemia, local ulceration and/or gastric hemorrhage have been described caused by high doses of ASA in Guinea pigs, rats, dogs, humans and other species. Doses have not been specified (Collier, 1969; Adv Pharmacol Chemother 7, 333-405). No other reports of spontaneous bleeding are available.

In conclusion, since the therapeutic dose for humans is significantly lower, the aforementioned toxic effects of both Clopidogrel and ASA are not relevant.

Genotoxicity

Clopidogrel

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

ASA

ASA did not show any evidence of mutagenic or clastogenic activity *in vitro*. There are no reports on *in vivo* genotoxicity tests.

Carcinogenicity

Clopidogrel

At doses of Clopidogrel of at least 25 times the human therapeutic dose, no carcinogenic effects were observed in rats after 104 weeks of treatment nor in mice after 78 weeks of treatment.

ASA

No carcinogenic effects of ASA could be demonstrated in mice after administration of 2 to 20 times the maximum tolerated clinical dose in mice for up to one year.

Reproductive and developmental toxicity

Clopidogrel

At doses up to 500 and 300 mg/kg/day Clopidogrel, no teratogenic or foetotoxic effects have been reported. A slight delay of development of the offspring of treated lactating rats has been reported due to a direct toxic effect or an indirect effect (low palatability).

ASA

At doses of 130 mg/kg/day ASA, infertility rate reached 8 times (40.5 %) the control group in the 5th generation of mice. The number of pups raised to weaning at 130 mg/kg/day reduced to one third the number raised by the controls and reduced dramatically with increasing dose (625-1270 mg/kg/day).

In rabbits, at doses of 500 mg/kg for 24 h on day 8-9 or day 9-10 of pregnancy, ASA induces cleft lip. When administered at day 12-13, day 13-14 or day 13 alone, no increase of clefts of the secondary palate was observed.

In rats, the NOEL of ASA was 80 mg/kg/d, which is around and about 10 times the therapeutic dose.

In conclusion, Clopidogrel/ASA should not be given during pregnancy. Breast feeding should be discontinued during treatment. This is adequately addressed in the Product Information.

2.2.4. Ecotoxicity/environmental risk assessment

Combination products of Clopidogrel/ASA are marketed for several years. The environmental risk assessment consisted of the determination of the PNEC for both substances. These studies were performed according to GLP.

The applicant provided adequate consumption data of Clopidogrel/ASA. A marked effect of improved adherence to therapy of the fixed combination product on the environmental exposure of clopidogrel bisulfate and acetylsalicylic acid is not expected.

2.2.5. Discussion on non-clinical aspects

Referring to published studies in animals, in men and *in vitro* models, pharmacological and toxicological features of Clopidogrel/ASA are well known. Moreover, both compounds have been extensively used in

humans in monotherapy as well as in combination. Following this and since there is no evidence to suggest negative interactions between Clopidogrel/ASA, no supplementary studies with the combination are required.

Taken into account the reproductive toxicity effects arising from ASA during early (embryofetal malformation) and late pregnancy (dystocia and foetal death), it is indicated that Clopidogrel/Acetylsalicylic acid should not be used during pregnancy as a precautionary measure. This is appropriately indicated in section 4.6 of the SmPC. Further, since it is unknown whether clopidogrel is excreted in human milk and since ASA is known to be excreted in human milk, breast-feeding should not be continued during treatment with Clopidogrel/ASA.

Concerning the environmental risk assessment, reliable data on consumption of Clopidogrel/ASA are provided to demonstrate that no increase in environmental exposure is expected. From non-clinical point of view, no further studies are asked.

2.2.6. Conclusion on the non-clinical aspects

In conclusion, referring to the low oral toxicity of Clopidogrel and ASA and to the extensive use of its combination in humans, no further studies concerning pharmacology, pharmacokinetics and toxicology are asked.

The non clinical data provided are considered adequate to support the clinical use.

2.3. Clinical aspects

2.3.1. Introduction

Acute coronary syndrome (ACS) is a clinical syndrome of acute cardiac ischemia related to coronary artery disease (CAD). The ACS continuum representing ongoing myocardial ischemia or injury consists of unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and STsegment elevation myocardial infarction (STEMI).

In terms of pathology, ACS is commonly associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery. Approximately 90% of myocardial infarctions (MIs) result from an acute thrombus that obstructs an atherosclerotic coronary artery. Plaque rupture and erosion are considered to be the major triggers for coronary thrombosis. Following plaque erosion or rupture, platelet activation and aggregation, coagulation pathway activation, and endothelial vasoconstriction occur, leading to coronary thrombosis and occlusion.

ACS can also be produced by elevated demand in the presence of a high-grade fixed coronary obstruction, due to increased myocardial oxygen and nutrition requirements, such as those resulting from exertion, emotional stress, or physiologic stress (e.g., from dehydration, blood loss, hypotension, infection, thyrotoxicosis, or surgery).

This Marketing Authorisation Application concerns clopidogrel/acetylsalicylic acid tablets containing clopidogrel (75 mg) and acetylsalicylic acid (ASA) (75 mg or 100 mg).

Clopidogrel / Acetylsalicylic acid Teva is a fixed dose combination formulated as a substitution therapy used in prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). This is used for continuation of therapy in non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention and in ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

The use of a fixed-dose combination tablet instead of the individual administration of the two compounds is expected to be more convenient to patients (and thus to improve compliance) by limiting the number of tablets they need to take.

The clinical development program consists of two bioequivalence studies with the objective to demonstrate the bioequivalence between Clopidogrel / Acetylsalicylic acid Teva 75/75 mg and 75/100 mg tablets (Teva Pharmaceutical Industries Ltd., Israel) and the free combination of clopidogrel and acetylsalicylic acid .

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type Study	Study Identifier	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
BE	BE study 1 2011-2626	The objective of this study is to evaluate the comparative bioavailability between: <ul style="list-style-type: none"> • Clopidogrel and Acetylsalicylic Acid 75/75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and • ASS gamma® 75 mg Tablets (Worwag Pharma GmbH & Co. KG, Germany) administered with • Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) after a single-dose in healthy subjects under fasting conditions. 	Open-label, single-dose, randomized, four-period, two-sequence, two-treatment, replicate, crossover study	Single 75 mg/75 mg tablet orally under fasting conditions	60	Healthy Subjects	Single dose treatment	Complete
BE	BE study 22011-2627	The objective of this study is to evaluate the comparative bioavailability between: <ul style="list-style-type: none"> • Clopidogrel and Acetylsalicylic Acid 75/100 mg Tablets (Teva Pharmaceutical Industries Ltd.) and • Aspirin® N 100 mg Tablets (Bayer Vital GmbH, Germany) administered with • Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers 	Open-label Single-dose, randomized, four-period, two-sequence, two-treatment, replicate, crossover study	Single 75 mg/100 mg tablet orally under fasting conditions	60	Healthy Subjects	Single dose treatment	Complete

		Squibb SNC, France) after a single-dose in healthy subjects under fasting conditions.						
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The two studies are open-label, randomized, four-period, two-sequence, two-treatment, single oral dose, crossover BE studies under fasting conditions.

2.3.2. Pharmacokinetics

2.3.2.1. Background information

- Clpidogrel

Clpidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%.

Clpidogrel is extensively metabolised in the liver, mainly to its inactive carboxylic acid derivative and its active metabolite, clpidogrel thiol.

Clpidogrel and its carboxylic acid metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively) in a nonsaturable manner at concentrations ≤ 100 mg/l

The elimination half-life of the carboxylic acid metabolite is about 7–8 hours after single-dose and repeated daily administration of clpidogrel. Clpidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

- Acetylsalicylic acid

Acetylsalicylic acid is rapidly absorbed after oral doses.

Following oral administration acetylsalicylic acid is partially hydrolysed to salicylate during absorption by esterases in the gastrointestinal mucosa. Following absorption unhydrolysed acetylsalicylic acid is rapidly and almost completely hydrolysed by esterases principally in the liver but also in plasma, erythrocytes and synovial fluid.

Salicylic acid is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, the ether or phenolic glucuronide, the ester or acyl glucuronide, gentisic acid, and other hydroxybenzoic acids

ASA is poorly bound to serum proteins (up to 33%) and binding of salicylic acid to plasma proteins depends on the concentration – it is 90-95% at concentrations of around 100 $\mu\text{g/mL}$ (which is around 2-fold higher than achieved with oral ASA doses of up to 325 mg) and decreases at higher concentrations.

Elimination of ASA is almost exclusively by hydrolysis to salicylic acid (around 1% of ASA dose is excreted unhydrolyzed by the kidney) and starts already in the gut wall.

Elimination of acetylsalicylic acid is a first-order process at concentrations in the range between 100-300 $\mu\text{g/mL}$ with a half-life of around 2- 3 hours.

2.3.2.2. Bioequivalence study

2.3.2.2.1. Methodology – Study design

This is an open-label, randomized, four-period, two-sequence, two-treatment, single oral dose, crossover BE study under fasting conditions.

- **Treatments**

Test product (Treatment A):

Clopidogrel/Acetylsalicylic Acid 75/75 mg tablets (Teva Pharmaceutical Industries Ltd., Israel).

Batch No.: K-45878

Potency: Clopidogrel: 98.6 % of label claim

Acetylsalicylic acid: 98.5 % of label claim

Manufacturing Date: 07/04/2011

Dose: One combination tablet (75 mg Clopidogrel and 75 mg Acetylsalicylic Acid)

Mode of Administration: Oral under fasting conditions

Batch size : 150,000 tablets.

Reference Product 1 (Treatment B):

ASS gamma® 75 mg tablets (Worwag Pharma GmbH & Co. KG, Germany)

Batch No.: 0710124 A

Potency: 100.7 % of label claim

Expiration Date: 09/2012

with

Reference Product 2 (Treatment B):

Plavix® 75 mg tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Batch No.: EN318

Potency: 98.4 % of label claim

Expiration Date: 11/2012

Dose: Two tablets (one tablet ASS gamma® 75 mg with one tablet Plavix®) 75 mg in a single oral dose

Mode of Administration: Oral under fasting conditions

- **Population studied**

A total of 60 subjects (35 males and 25 females) were included into the study. Only 56 completed both treatment periods of this study

- **Analytical methods**

Clopidogrel

For the two studies (2011-2626 and 2011-2627), the plasma concentrations of free clopidogrel in the study samples were quantified by a validated LC/MS/MS method after a liquid-liquid extraction using clopidogrel rac-d4 hydrogen sulfate as the internal standard.

The analytical method used has been shown to be sensitive, accurate and selective for the plasma level determination of clopidogrel in the concentration range of 0.01000-10 ng/mL.

Concerning the validation of the bioanalytical method, information on the characteristics of linearity, within- and between-run accuracy and precision, recovery, selectivity, dilution integrity, matrix effect, hemolysis effect, re-injection reproducibility, short and long term stability are described.

Acetylsalicylic acid

For the two studies, the plasma concentrations of free acetylsalicylic acid and salicylic acid in the study samples were quantified by a validated LC/MS/MS method after a liquid-liquid extraction using 2-acetoxybenzoic-3,4,5,6-d4 acid as internal standard for the determination of acetylsalicylic acid and 2-hydroxybenzoic-3,4,5,6-d4 acid as internal standard for the determination of salicylic acid.

The analytical method used has been shown to be sensitive, accurate and selective for the plasma level determination of acetylsalicylic acid in the concentration range of 10.0-5000 ng/mL and for the plasma level determination of salicylic acid in the concentration range of 50.0-10000 ng/mL.

Concerning the validation of the bioanalytical method, information on the characteristics of linearity, within- and between-run accuracy and precision, recovery, selectivity, dilution integrity, matrix effect, hemolysis effect, re-injection reproducibility, short and long term stability are described.

- **Statistical methods**

ANOVA was performed on ln-transformed AUC_{0-t} and C_{max} for clopidogrel, acetylsalicylic acid and salicylic acid.

A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the T_{max} between treatments. Ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC_{0-t} and C_{max}.

2.3.2.2.2. Study results

Table 2: Results of the pharmacokinetic and statistical analysis of clopidogrel

Parameter	Irt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%) (A-B)	Intra-Sbj CV(%) (B1-B2)	Wider BE Range (%)
C _{max} (ng/mL)	A1	58	1.8019 (145)	1.0940	A vs B	100.85	92.91-109.47	39	38	75.68-132.14
	A2	58	2.0534 (118)							
	B1	58	2.0150 (166)	1.0848						
	B2	57	2.0630 (135)							
AUC _t (ng.h/mL)	A1	58	2.6128 (133)	1.5527	A vs B	99.62	92.35-107.47	36	N/A	N/A
	A2	58	2.9589 (136)							
	B1	58	2.6386 (139)	1.5586						
	B2	56	2.7270 (123)							
T _{max} (h)	A1	58	0.78 (97)							
	A2	58	0.61 (39)							
	B1	58	0.76 (43)							
	B2	57	0.74 (35)							
			<i>Median</i>	<i>Range</i>						
T _{max} (h)	A1	58	0.58	0.17-5.00						
	A2	58	0.58	0.17-1.25						
	B1	58	0.67	0.33-2.50						
	B2	57	0.67	0.33-1.75						

Treatments A1 & A2: Clopidogrel and Acetylsalicylic acid 75/75 mg Tablets (Teva Pharmaceutical Industries Ltd.)
Treatments B1 & B2: ASS gamma® 75 mg Tablets (Worwag Pharma GmbH & Co. KG , Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Table 3: Results of the pharmacokinetic and statistical analysis of acetylsalicylic acid (36 subjects)

<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
C_{max} (ng/mL)	A	36	1234.2 (27)	1199.1	A vs B	118.65	110.34 - 127.59	18
	B	36	1084.3 (38)	1010.6				
AUC_t (ng.h/mL)	A	36	1071.0 (27)	1035.7	A vs B	102.02	97.40 - 106.86	12
	B	36	1050.2 (26)	1015.1				
T_{max} (h)	A	36	0.55 (26)					
	B	36	0.64 (34)					
			<i>Median</i>	<i>Range</i>				
T_{max} (h)	A	36	0.58	0.17- 0.83				
	B	36	0.58	0.50- 1.75				

Treatment A: Clopidogrel and Acetylsalicylic acid 75/75 mg Tablets (Teva Pharmaceutical Industries Ltd.)

Treatment B: ASS gamma® 75 mg Tablets (Worwag Pharma GmbH & Co. KG, Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Table 4: Results of the pharmacokinetic and statistical analysis of salicylic acid (36 subjects)

<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
C_{max} (ng/mL)	A	36	4571.9 (21)	4468.8	A vs B	104.96	100.75 - 109.34	10
	B	36	4363.3 (23)	4257.8				
AUC_t (ng.h/mL)	A	36	17774.1 (31)	17005.8	A vs B	101.11	98.50 - 103.79	7
	B	36	17585.5 (32)	16818.9				
T_{max} (h)	A	36	1.18 (20)					
	B	36	1.41 (34)					
			<i>Median</i>	<i>Range</i>				
T_{max} (h)	A	36	1.25	0.83- 1.75				
	B	36	1.25	0.83- 2.50				

Treatment A: Clopidogrel and Acetylsalicylic acid 75/75 mg Tablets (Teva Pharmaceutical Industries Ltd.)

Treatment B: ASS gamma® 75 mg Tablets (Worwag Pharma GmbH & Co. KG, Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Safety data

A total of 64 post-dose adverse events were reported by 25 of the 60 subjects who received at least one dose of the study medication (safety population). Among these adverse event, 61 were graded as mild and 3 were graded as moderate. No deaths or serious adverse events were reported during the conduct of the trial.

2.3.2.3. Bioequivalence study 2

2.3.2.3.1. Methodology – Study design

This is an open-label, randomized, four-period, two-sequence, two-treatment, single oral dose, crossover BE study under fasting conditions.

- **Treatments**

Test product (Treatment A):

Clopidogrel/Acetylsalicylic Acid 75/100 mg tablets (Teva Pharmaceutical Industries Ltd., Israel).
Batch No.: K-45939
Potency: Clopidogrel: 101.5 % of label claim
Acetylsalicylic acid: 100.9 % of label claim
Manufacturing Date: 12/04/2011
Dose: One combination tablet (75 mg Clopidogrel and 100 mg Acetylsalicylic Acid)
Mode of Administration: Oral under fasting conditions
Batch size : 150,000 tablets.

Reference Product 1 (Treatment B):

Aspirin® N 100 mg tablets (Bayer Vital GmbH, Germany)
Batch No.: BTA9F60
Potency: 104.4 % of label claim
Expiration Date: 03/2015

with

Reference Product 2 (Treatment B):

Plavix® 75 mg tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)
Batch No.: EN318
Potency: 98.4 % of label claim
Expiration Date: 11/2012

Dose: Two tablets (one tablet Aspirin® N 100 mg with one tablet Plavix® 75 mg) in a single oral dose
Mode of Administration: Oral under fasting conditions

- **Population studied**

A total of 60 subjects (30 males and 30 females) were included into the study. Only 52 completed both treatment periods of this study.

- **Analytical methods and statistical analysis**

See above description for Bioequivalence study 1.

2.3.2.3.2. Study results

Table 5: Results of the pharmacokinetic and statistical analysis of clopidogrel

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%) (A-B)	Intra-Sbj CV(%) (B1-B2)	Wider BE Range (%)
C_{max} (ng/mL)	A1	57	1.5607 (149)	0.8929	A vs B	102.29	93.06-112.44	44	49	70.46-141.93
	A2	55	1.7975 (142)							
	B1	57	1.4295 (122)							
	B2	52	1.7725 (184)							
AUC_t (ng.h/mL)	A1	57	1.9610 (119)	1.2107	A vs B	95.89	88.39-104.03	38	N/A	N/A
	A2	55	2.1493 (127)							
	B1	57	1.9880 (121)							
	B2	52	2.1138 (119)							
T_{max} (h)	A1	57	0.67 (30)	-	-	-	-	-	-	-
	A2	55	0.64 (40)							
	B1	57	0.76 (31)							
	B2	52	0.73 (28)							
			<i>Median</i>	<i>Range</i>						
T_{max} (h)	A1	57	0.67	0.33-1.25	-	-	-	-	-	-
	A2	55	0.58	0.33-1.75	-	-	-	-	-	-
	B1	57	0.67	0.33-1.50	-	-	-	-	-	-
	B2	52	0.75	0.33-1.50	-	-	-	-	-	-

Treatments A1 & A2: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets (Teva Pharmaceutical Industries Ltd.)
Treatments B1 & B2: Aspirin® N 100 mg Tablets (Bayer Vital GmbH , Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Table 6: Results of the pharmacokinetic and statistical analysis of acetylsalicylic acid (36 subjects)

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
C_{max} (ng/mL)	A	36	1656.6 (28)	1594.5	A vs B	101.10	94.53 - 108.14	17
	B	36	1655.1 (31)	1577.1				
AUC_t (ng.h/mL)	A	36	1471.1 (29)	1412.8	A vs B	92.62	88.34 - 97.11	12
	B	36	1571.9 (25)	1525.3				
T_{max} (h)	A	36	0.54 (26)	-	-	-	-	-
	B	36	0.61 (28)					
			<i>Median</i>	<i>Range</i>				
T_{max} (h)	A	36	0.50	0.33- 0.83	-	-	-	-
	B	36	0.58	0.33- 1.00	-	-	-	-

Treatment A: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets (Teva Pharmaceutical Industries Ltd.)
Treatment B: Aspirin® N 100 mg Tablets (Bayer Vital GmbH , Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Table 7: Results of the pharmacokinetic and statistical analysis of salicylic acid (36 subjects)

<i>Parameter</i>	<i>Trt</i>	<i>n</i>	<i>Arithmetic Mean (CV%)</i>	<i>Geometric Mean</i>	<i>Contrast</i>	<i>Ratio (%)</i>	<i>90% Confidence Interval</i>	<i>Intra-Sbj CV(%)</i>
C_{max} (ng/mL)	A	36	6198.6 (18)	6099.7	A vs B	100.48	96.32 - 104.82	11
	B	36	6212.5 (22)	6070.4	-	-	-	-
AUC_t (ng.h/mL)	A	36	24514.6 (30)	23658.9	A vs B	96.11	94.19 - 98.07	5
	B	36	25597.0 (31)	24616.4	-	-	-	-
T_{max} (h)	A	36	1.14 (27)	-	-	-	-	-
	B	36	1.41 (31)	-	-	-	-	-
			<i>Median</i>	<i>Range</i>				
T_{max} (h)	A	36	1.01	0.83- 2.50	-	-	-	-
	B	36	1.38	0.67- 3.00	-	-	-	-

Treatment A: Clopidogrel and Acetylsalicylic acid 75/100 mg Tablets (Teva Pharmaceutical Industries Ltd.)

Treatment B: Aspirin® N 100 mg Tablets (Bayer Vital GmbH , Germany) with Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France)

Safety data

A total of 77 post-dose adverse events were reported by 26 of the 60 subjects who received at least one dose of the study medication (safety population). All the 77 post-dose adverse events reported were graded as mild. No deaths or serious adverse events were reported during the conduct of the trial.

Pharmacokinetic Conclusion

From these results, it can be concluded that Clopidogrel/Acetylsalicylic Acid 75/75 mg tablets are bioequivalent to the concomitant administration of ASS gamma® 75 mg tablets tablets and Plavix® 75 mg tablets as well as Clopidogrel/Acetylsalicylic Acid 75/100 mg tablets are bioequivalent to Aspirin® N 100 mg tablets and Plavix® 75 mg tablets, with respect to rate and extent of absorption.

2.3.3. Pharmacodynamics

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

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo oxygenase and thus inhibits the generation of thromboxane A₂, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

2.3.4. Discussion and conclusion on clinical pharmacology

This application concerns a fixed dose combination of clopidogrel and acetylsalicylic acid (ASA) and the following strengths are proposed for this FDC: clopidogrel/ASA 75mg/75mg and 75mg/100mg. In this context, two bioequivalence studies were conducted.

Both bioequivalence studies were identical in design and consist in an open-label, randomized, four-period, two-sequence, two-treatment, single oral dose, crossover design under fasting conditions. The fasting state is acceptable since the mono-therapy products can be taken with or without food. The applicant chose to conduct a replicate design bioequivalence study: data from 4 periods were analysed for clopidogrel since it was expected to be highly variable, data from period 1 and 2 were analysed for salicylic acid and ASA.

Bioequivalence was investigated for both strengths based on the clopidogrel and acetylsalicylic acid data. In the study with the lower strength the 90%CI for acetylsalicylic acid's C_{max} around the point estimate was 110.34 – 127.59%, exceeding the standard bioequivalence range. The 90% confidence intervals around the point estimate of AUC_t for ASA was within the standard bioequivalence range. It was pre-specified in the protocol that ASA data would be analysed for information only. This approach is considered acceptable since ASA has a half-life less than 1 hour. Wider 90%CI for the C_{max} of ASA has been previously accepted by the CHMP during the authorisation of DuoCover/DuoPlavin (fixed dose combination of clopidogrel/ASA 75mg/100mg and 75mg/75mg).

Based on these results, bioequivalence is considered as demonstrated between Clopidogrel/Acetylsalicylic Acid 75/75 mg tablets and ASS gamma® 75 mg tablets and Plavix® 75 mg tablets and between Clopidogrel/Acetylsalicylic Acid 75/100 mg tablets and Aspirin® N 100 mg tablets and Plavix® 75 mg tablets with respect to rate and extent of absorption under fasting conditions.

The potential for PK interaction between clopidogrel and ASA has not been assessed in humans but is based on the PK characteristics of clopidogrel and ASA and on the drug-drug interaction profiles of each of these drugs. The potential for pharmacokinetic interaction between clopidogrel and ASA is deemed unlikely.

ASA and clopidogrel have a synergistic antiplatelet effect as both affect platelet aggregation by different mechanisms, thus the combination is well justified. The mechanism of action of both substances are well known. The Applicant provides a thorough bibliographic review on the pharmacodynamics of clopidogrel and ASA.

There are no outstanding issues on pharmacokinetics and pharmacodynamics.

2.4. Clinical efficacy

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

The CURE study included 12,562 patients with non ST segment elevation acute coronary syndrome (unstable angina or non-Q wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) plus ASA (75 325 mg once daily) or ASA alone (N=6,303), (75 325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in

more than 90% of the patients and the relative rate of bleeding between clopidogrel plus ASA and ASA alone was not significantly affected by the concomitant heparin therapy.

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

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

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

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

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

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

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

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

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

2.4.1. Discussion and conclusions on clinical efficacy

Clopidogrel / Acetylsalicylic acid Teva is a fixed dose combination formulated as a substitution therapy used in prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). This is used for continuation of therapy in non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention and in ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

The combined use of these active substances can be considered well recognised and adequately demonstrated. The review on the available efficacy data proves that clopidogrel and ASA both decrease vascular events and each component apart contributes to this effect.

The most important trials are CURE, CLARITY-TIMI and COMMIT. The applicant provided adequate information supporting the efficacy of the combination and its use in combination as a fixed-dose combination tablet instead of the individual administration of the two compounds. The combination clopidogrel/ASA is expected to be more convenient to patients and thus to improve compliance by limiting the number of tablets they need to take.

2.5. Clinical safety

Summary of the safety profile

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are discussed below. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

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

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

In CURE there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients

who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

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

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

Tabulated list of adverse reactions

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

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), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Anaphylactic shock*, serum sickness, anaphylactoid reactions, aggravation of allergic symptoms of food allergy*
Metabolism and nutrition disorders				Hypoglycaemia*, gout* (see section 4.4)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	Hearing loss* or tinnitus*
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal	Epistaxis			Respiratory tract bleeding (haemoptysis,

System Organ Class	Common	Uncommon	Rare	Very rare, not known
disorders				pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, gastro-duodenal ulcer/perforations*, colitis (including ulcerative or lymphocytic colitis), upper gastro-intestinal symptoms* such as gastralgia (see section 4.4), stomatitis
Hepatobiliary disorders				Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic enzymes*, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal and connective tissue disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)*, glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at the puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

* Information reported in published information for ASA (frequency "not known").

2.4.1. Discussion on clinical safety

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are discussed above. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

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

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

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

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

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

2.4.2. Conclusions on clinical safety

The combined use of these active substances can be adequately demonstrated and well known.

The most important safety problem is bleeding. This is linked with the mechanism of action of both substances. Another problem is thrombotic thrombocytopenic purpura. It has been estimated that there are about four cases in every million patients.

Both the safety of ASA and Clopidogrel have been well analysed in the bibliographic review provided in support of this application. No new safety studies have been performed which is considered acceptable.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.5. Risk Management Plan

The CHMP received the following PRAC Advice on the version 1.2 of the revised Risk Management Plan:

The proposed RMP is acceptable. The advice was based upon the following RMP parts:

Safety concerns

Table 1. Summary of safety concerns

<ul style="list-style-type: none">• IMPORTANT IDENTIFIED RISKS	<ul style="list-style-type: none">• Bleeding and haematological disorders• Increased risk of bleeding (in combination with other antiplatelet agents or other medicinal products acting on hemostasis, in pathologic conditions as trauma and surgery, in patients with recent transient ischaemic attack or stroke or with a history of peptic ulcer/gastroduodenal haemorrhage or minor upper GI symptoms)• Thrombotic thrombocytopenic purpura (TTP) (due to clopidogrel)• Hypersensitivity reactions• Reduced efficacy of clopidogrel in poor CYP2C19 metabolisers• Aggravation of gout (due to ASA)• Hepatotoxicity (due to ASA)• Impaired renal function (due to ASA)• Eosinophilic pneumonia (due to clopidogrel)• Bone marrow toxicity due to interaction with methotrexate
<ul style="list-style-type: none">• IMPORTANT POTENTIAL RISKS	<ul style="list-style-type: none">• Reye' s syndrome in children < 18 years of age (due to ASA)• Reduced efficacy of clopidogrel when strong or moderate inhibitors of CYP2C19 are used concomitantly
<ul style="list-style-type: none">• MISSING INFORMATION	<ul style="list-style-type: none">• Use during pregnancy and breastfeeding• Interaction between ASA and NSAIDs

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Bleeding and haematological disorders	<p>Labelling information presented in the following SmPC sections:</p> <p>Contraindication in Section 4.3: in case active pathological bleeding such as peptic ulcer;</p> <p>Section 4.4, SmPC: Special warnings and precautions for use regarding bleeding and haematological disorders, recent transient ischaemic attack or stroke, gastrointestinal (GI).</p> <p>Listed in section 4.8: The incidence of bleeding from studies CAPRIE, CURE CLARITY, and COMMIT. Haematoma, Epistaxis, Gastrointestinal haemorrhage, Bruising, Bleeding at the puncture site are listed as common ADRs ($\geq 1/100$ to $< 1/10$).</p> <p>Intracranial bleeding (some cases were reported with fatal outcome), eye bleeding (conjunctival, ocular, retinal), bleeding time prolonged, haematuria, and skin bleeding (purpura) are listed as uncommon ADRs ($\geq 1/1,000$ to $< 1/100$).</p> <p>Retroperitoneal haemorrhage is listed as rare ADR ($\geq 1/10,000$ to $< 1/1,000$).</p> <p>Serious haemorrhage, haemorrhage of operative wound, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), gastrointestinal and retroperitoneal haemorrhage with fatal outcome, and musculo-skeletal bleeding (haemarthrosis) are listed with very rare frequency.</p> <p>Risk of bleeding due to overdose in Section 4.9.</p> <p>Prescription-only medicine</p>	Not applicable
Increased risk of bleeding (in combination with	Labelling information presented in the following SmPC sections:	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
<p>other antiplatelet agents or other medicinal products acting on hemostasis, in pathologic conditions as trauma and surgery, in patients with recent transient ischaemic attack or stroke or with a history of peptic ulcer/gastroduodenal haemorrhage or minor upper GI symptoms)</p>	<p>Contraindication in Section 4.3: in case active pathological bleeding such as peptic ulcer;</p> <p>Warning in section 4.4 that clopidogrel/ASA should be used with caution in patients receiving treatment with other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or thrombolytics; Special warnings and precautions for use regarding bleeding and haematological disorders, surgery, recent transient ischaemic attack or stroke, gastrointestinal (GI).</p> <p>Interactions with NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or thrombolytics listed in section 4.5.</p> <p>Prescription-only medicine</p>	
<p>Thrombotic thrombocytopenic purpura (TTP)</p>	<p>Labelling information presented in the following SmPC sections</p> <p>Section 4.4, SmPC: Special warnings and precautions for use regarding Thrombotic Thrombocytopenic Purpura (TTP).</p> <p>Listed in section 4.8: Thrombotic thrombocytopenic purpura (TTP) is listed as very rare ADRs</p> <p>Prescription-only medicine</p>	Not applicable
<p>Hypersensitivity reactions</p>	<p>Labelling information presented in the following SmPC sections</p> <p>Section 4.3 Contraindications, SmPC: Due to the presence of ASA, use is contraindicated in hypersensitivity to NSAIDs and syndrome of asthma, rhinitis, nasal polyps, and pre-existing mastocytosis</p> <p>Section 4.4, special warnings and precautions for use, SmPC: Caution required due to ASA in patients with a history of asthma or allergic disorders. Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since</p>	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>allergic cross-reactivity among thienopyridines has been reported.</p> <p>Listed in section 4.8: Serum sickness and anaphylactoid reactions are listed as very rare (<1/10,000) ADRs of clopidogrel/ASA. Anaphylactic shock and aggravation of allergic symptoms of food allergy were reported in published information for ASA with frequency "not known". Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) is related to clopidogrel with frequency "not known".</p> <p>Bullous dermatitis (Toxic Epidermal Necrolysis TEN, Stevens Johnson Syndrome SJS, erythema multiforme), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS) are listed as very rare (<1/10,000) ADRs of clopidogrel/ASA.</p> <p>Prescription-only medicine</p>	
<p>Reduced efficacy of clopidogrel in poor CYP2C19 metabolisers</p>	<p>Labelling information presented in the following SmPC sections</p> <p>Section 4.4, SmPC: Special warnings and precautions for use regarding Cytochrome P450 2C19 (CYP2C19) pharmacogenetics.</p> <p><i>Pharmacogenetics information about CYP2C19 is given in Section 5.2, SmPC:</i></p> <p>Prescription-only medicine</p>	<p>Not applicable</p>
<p>Aggravation of gout (due to ASA)</p>	<p>Labelling information presented in the following SmPC sections</p> <p>Section 4.4, special warnings and precautions for use, SmPC: Caution required due to ASA in patients with gout.</p> <p>Listed in section 4.8, SmPC: Gout was reported in published information for ASA with frequency "not known".</p> <p>Prescription-only medicine</p>	<p>Not applicable</p>
<p>Hepatotoxicity (due to ASA)</p>	<p>Labelling information presented in the following SmPC sections</p> <p>Contraindication for severe impairment in</p>	<p>Not applicable</p>

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>4.3; Listed in section 4.8: Acute liver failure, hepatitis, and abnormal liver function test are listed as very rare (<1/10,000) ADRs of clopidogrel/ASA. Liver injury, mainly hepatocellular, and elevation of hepatic enzymes were reported in published information for ASA with frequency "not known".</p> <p>Prescription-only medicine</p>	
Impaired renal function (due to ASA)	<p>Labelling information presented in the following SmPC sections</p> <p>Posology for use in renal impairment in Section 4.2; Contraindication for severe renal impairment in 4.3; Listed in section 4.8: Glomerulonephritis and blood creatinine increased are listed as very rare (<1/10,000) ADRs of clopidogrel/ASA.</p> <p>Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics) was reported in published information for ASA with frequency "not known".</p> <p>Prescription-only medicine</p>	Not applicable
Eosinophilic pneumonia (due to clopidogrel)	<p>Labelling information presented in the following SmPC sections</p> <p>Listed in section 4.8: Eosinophilic pneumonia is listed as very rare (<1/10,000) ADR of clopidogrel/ASA.</p> <p>Prescription-only medicine</p>	Not applicable
Bone marrow toxicity due to interaction with methotrexate	<p>Labelling information presented in the following SmPC section:</p> <p>Warning for cautious concomitant use with methotrexate is given in section 4.5, interaction with other medicinal products and other forms of interaction</p> <p>Prescription-only medicine</p>	Not applicable
IMPORTANT POTENTIAL RISKS		
Reye's syndrome in children < 18 years of age (due to ASA)	<p>Labelling information presented in the following SmPC sections</p> <p>Section 4.2 Clopidogrel is not recommended in children and adolescents</p>	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	under 18 years. Section 4.4, special warnings and precautions for use, SmPC: Caution required due to ASA in children under 18 years of age. Prescription-only medicine	
Reduced efficacy of clopidogrel when strong or moderate inhibitors of CYP2C19 are used concomitantly	Labelling information presented in the following SmPC sections Section 4.4, SmPC: Special warnings and precautions for use regarding strong or moderate inhibitors of Cytochrome P450 2C19 (CYP2C19). Section 4.5, interaction with other medicinal products and other forms of interaction, SmPC: Information regarding strong or moderate inhibitors of Cytochrome P450 2C19 (CYP2C19). Prescription-only medicine	Not applicable
MISSING INFORMATION		
Use during pregnancy and breastfeeding	Labelling information presented in the following SmPC sections Contraindication in Third trimester of pregnancy in Section 4.3; Warning and available information in section 4.8. Prescription-only medicine	Not applicable
Interaction between ASA and NSAIDs	Labelling information presented in the following SmPC sections Warning on cautious use with other NSAIDs including Cox 2 inhibitors in Section 4.4 Information that experimental data suggest that ibuprofen may inhibit the effect of low dose ASA is given in Sections 4.5 and 5.1. Prescription-only medicine	Not applicable

The CHMP endorses the PRAC advice without changes.

2.8. Product information

2.5.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

Clopidogrel / Acetylsalicylic acid Teva is a fixed dose combination formulated as a substitution therapy used in prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). This is used for continuation of therapy in non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention and in ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

The most important trials are CURE, CLARITY-TIMI and COMMIT. The applicant provided adequate information supporting the efficacy of the combination and its use in combination as a fixed-dose combination tablet instead of the individual administration of the two compounds. The combination clopidogrel/ASA is expected to be more convenient to patients and thus to improve compliance by limiting the number of tablets they need to take.

In the CURE trial, the number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel plus ASA group and 719 (11.4%) in the ASA group, a 20% relative risk reduction (RRR) (95% CI of 10% 28%; $p=0.00009$) for the clopidogrel plus ASA group. New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively.

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

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

The combined use of these active substances can be considered well recognised and adequately demonstrated.

This fixed combination can improve the compliance because patients will have to take only one tablet instead of two.

Uncertainty in the knowledge about the beneficial effects

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

There is still uncertainty if the beneficial effects are maintained on the very long term which was not tested in clinical trials.

The efficacy of clopidogrel/acetylsalicylic acid in children and adolescents under 18 years old have not been established. The combination of clopidogrel/acetylsalicylic acid is not recommended in this population.

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

- In patients with ST segment elevation acute myocardial infarction: Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting. If the use of

the combination of clopidogrel/acetylsalicylic acid is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

Therapeutic experience is limited in patients with mild to moderate renal impairment.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Risks

Unfavourable effects

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

Another problem is thrombotic thrombocytopenic purpura. It has been estimated that there are about four cases in every million patients.

Uncertainty in the knowledge about the unfavourable effects

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more.

There is still uncertainty about the safety on the very long term which was not tested in clinical trials.

The safety of clopidogrel/acetylsalicylic acid in children and adolescents under 18 years old have not been established. The combination of clopidogrel/acetylsalicylic acid is not recommended in this population.

Therapeutic experience is limited in patients with mild to moderate renal impairment.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Balance

The favourable effect of clopidogrel/ASA to prevent ischaemic events outweighs the risk of bleeding.

Bleeding can be limited by excluding high risk patients and careful monitoring during treatment.

Ischaemic events cause irreversible damage.

Benefit-risk balance

The benefit/risk balance is positive.

Discussion on the benefit-risk assessment

A fixed dose combination of acetyl salicylic acid (ASA) and clopidogrel is proposed for a substitution indication in secondary cardiovascular prevention. Both individual components have been used long-term in this indication.

The company provides an overview of the use of both components of the proposed fixed dose combination.

In combination, both components exhibit superior efficacy compared to each component alone. This superior efficacy is counterbalanced by an increased risk of bleeding. In balance, it is generally accepted that patients at high cardiovascular risk benefit from the combination. This is established in a number of large scale trials (e.g. CURE, COMMIT and CLARITY) and a meta-analysis of use of the combination. The combination is recommended in current guidelines of the European Cardiology Society (ECS) on Acute Coronary Syndrome. The proposed SmPC reflects this long-standing experience.

Both components are well known with respect to their safety profile.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Clopidogrel/Acetylsalicylic acid Teva in *the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Fixed-dose combination medicinal product for continuation of therapy in:*

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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Medicinal product no longer authorised