14 November 2019
EMA/7091/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Clopidogrel/Acetylsalicylic acid Mylan

International non-proprietary name: clopidogrel / acetylsalicylic acid

Procedure No. EMEA/H/C/004996/0000

Note

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

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Administrative information

Name of the medicinal product:	Clopidogrel/Acetylsalicylic acid Mylan
Applicant:	Mylan S.A.S 117 Allee des Parcs 69800 Saint-Priest FRANCE
Active substances:	Acetylsalicylic acid / clopidogrel hydrogen sulfate
International non-proprietary name/Common name:	Clopidogrel / acetylsalicylic acid
Pharmaco-therapeutic group (ATC Code):	Antithrombotic agents, platelet aggregation inhibitors excl. heparin (B01AC30)
Therapeutic indication(s):	Clopidogrel/Acetylsalicylic acid Mylan is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Clopidogrel/Acetylsalicylic acid Mylan is a 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
Pharmaceutical form(s):	Film-coated tablet

Strength(s):	75 mg / 75 mg and 75 mg / 100 mg
Route(s) of administration:	Oral use
Packaging:	Blister (alu/alu) and bottle (HDPE)
Package size(s):	28 tablets, 28 x 1 tablet (unit dose), 30 tablets, 30 x 1 tablet (unit dose) and 100 tablets

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List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the curve
CEP	Certificate of Suitability of the European Pharmacopoeia
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRS	Chemical Reference Substance (official standard)
EEA	European Economic Area
EDTA	Ethylenediaminetetraacetic acid
GCP	Good clinical practice
HDPE	High-density polyethylene
HMLDPE	High molecular Low Density Polyethylene
HPLC	High Performance Liquid Chromatography
IR	Infrared
ISR	Incurred samples reanalysis
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDPE	Low-density polyethylene
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
NMT	Not more than
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
QC	Quality Control
RH	Relative Humidity
rpm	Rotations per minute
RSD	Relative standard deviation
$t_{1/2}$	Half-life
T_{max}	Time to maximum plasma concentration

TTC	Threshold of Toxicological Concern
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 14 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Clopidogrel/Acetylsalicylic acid Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union the basis of a complete dossier in accordance with Article 10b of Directive 2001/83/EC.

The applicant applied for the following indication:

Clopidogrel/Acetylsalicylic acid Mylan is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Clopidogrel/Acetylsalicylic acid Mylan is a 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:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product DuoPlavin instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: DuoPlavin 75 mg/75 mg and 75 mg/100 mg film-coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-03-2010
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/619/001-015

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: DuoPlavin 75 mg/75 mg and 75 mg/100 mg film-coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-03-2010
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/619/001-015

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Marketing authorisation number: EU/1/10/619/001-015
- Product name, strength, pharmaceutical form: DuoPlavin 75 mg/75 mg and 75 mg/100 mg film-coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-03-2010
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number: EU/1/10/619/001-015
- Bioavailability study number(s): BE study C18156

Information on paediatric requirements

Not applicable

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.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Rajko Kenda Co-Rapporteur : N/A

CHMP Peer reviewer: N/A

The application was received by the EMA on	14 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 January 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 April 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	4 and 9 September 2019
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	11 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	30 October and 7 November 2019
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 Mylan on	14 November 2019

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns Clopidogrel/Acetylsalicylic acid Mylan 75 mg/100 mg and 75 mg/75 mg film-coated tablets, a generic of DuoPlavin. The originator of Clopidogrel/Acetylsalicylic acid Mylan, DuoPlavin75 mg/75 mg and 75mg/100 mg film-coated tablets from Sanofi Pharma Bristol-Myers Squibb SNC is a fixed-dose combination of clopidogrel and acetylsalicylic acid. It was first approved in the EU in 2010 for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA) as continuation 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

Clopidogrel and acetylsalicylic acid are antithrombotic agents and platelet aggregation inhibitors. Clopidogrel selectively inhibits the binding of adenosine diphosphate to its platelet receptor and the subsequent adenosine diphosphate-mediated activation of the glycoprotein IIb/IIIa complex. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released adenosine diphosphate. Acetylsalicylic acid inhibits the thromboxane A2 formation due to the acetylation of the platelets cyclooxygenase. This anti-aggregate effect is irreversible during the platelets life. Acetylsalicylic acid has also analgesic and antipyretic effects; it inhibits the synthesis of prostaglandins and has possible central effects on the hypothalamus.

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.

This fixed-dose combination of antiplatelet agents is aimed to cover a substitution therapy of clopidogrel and ASA administered at the same dose level, dosing interval, and dose timing in the indications where the labeling of clopidogrel mentions it should be administered concomitantly with ASA [i.e., the prevention of atherothrombotic events in patients suffering from acute coronary syndrome (ACS): Non-ST-segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) and ST-segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy].

Both the test and the reference product contain the same active ingredients i.e. clopidogrel hydrogen sulfate and acetylsalicylic acid.

The Applicant for Clopidogrel/Acetylsalicylic acid Mylan is claiming the same indications as currently approved for DuoPlavin.

The applicant submitted an abridged application relying on the clinical data of the reference product and a bioequivalence study to establish essential similarity between the test product and the EU reference product.

The applicant has conducted one fasting bioequivalence study (study C18156) on the highest strength 75mg/100 mg and is requesting a biowaiver for the lower 75 mg/75 mg strength in accordance with the Guideline on the Investigation of bioequivalence.

The proposed indication is:

Clopidogrel/Acetylsalicylic acid Mylan is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Clopidogrel/Acetylsalicylic acid Mylan is a 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

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing a fixed-dose combination of 75 mg clopidogrel (as hydrogen sulfate) and 75 or 100 mg acetylsalicylic acid.

Other ingredients are:

- **Tablet core**: cellulose microcrystalline, lactose, croscarmellose sodium, hydroxypropylcellulose, colloidal anhydrous silica, talc, hydrogenated castor oil, pregelatinized starch, stearic acid, iron oxide yellow (E172)
- **Coating for 75 mg/75 mg film-coated tablets**: hypromellose, triacetin, talc, poly (vinyl alcohol) (partially hydrolysed), titanium dioxide, iron oxide yellow (E172), glycerol monocaprylocaprate Type 1, sodium lauril sulfate
- **Coating for 75 mg/100 mg film-coated tablets**: hypromellose, triacetin, talc, poly (vinyl alcohol) (partially hydrolysed), titanium dioxide, allura red AC (E129), glycerol monocaprylocaprate type 1, sodium lauril sulfate

The product is available in aluminium blisters with desiccant layer containing 28 or 30 film-coated tablets, aluminium perforated unit dose blisters with desiccant layer containing 28 or 30 film-coated tablets, or HDPE bottles with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant containing 100 film-coated tablets.

2.2.2. Active Substance

Clopidogrel hydrogen sulfate

General Information

The chemical name of clopidogrel hydrogen sulfate is methyl (2S)-(2-chlorophenyl)[6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]acetate sulfate, corresponding to the molecular formula C16H18ClNO6S2. It has a relative molecular mass of 419.9 and the following structure (Figure 1):

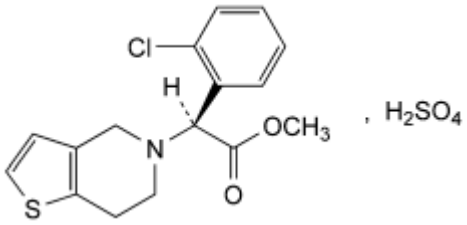

Figure 1 Clopidogrel hydrogen sulfate structure

Structure elucidation and chemical properties of active substance were documented via different analytical techniques; infrared spectrum (IR), ultraviolet spectrum (UV), proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR), mass spectrometry, elemental analysis and

Powder X-ray diffraction (PXRD).

Clopidogrel hydrogen sulfate is described in the Ph. Eur. (monograph 01/2017:2531). There is one manufacturer of the clopidogrel hydrogen sulfate active substance and the ASMF procedure is used.

Clopydogrel hydrogene sulfate is a white or almost white powder, freely soluble in methanol, slightly soluble in water and dichloromethane, practically insoluble in cyclohexane, acetone and ethyl acetate.

It is freely soluble in acidic conditions (pH 1.2) and soluble in the range from pH 4.5 to 8.0.

Clopidogrel hydrogen sulfate exists in two polymorphic forms (Form-I and Form-II).

The test for identification of polymorph by XRPD is part of active substance release and stability specifications. Based on the XRPD data of three consecutive production scale batches it is confirmed that the active substance manufacturer consistently produces the desired polymorphic form. Stability of the polymorphic form is confirmed by results of stability studies.

Clopidogrel hydrogen sulfate exhibits stereoisomerism due to the presence of one chiral centre. The active substance is the *S* (+) Isomer. The undesired isomer, *R*-isomer is controlled in the active substance specifications (by HPLC) with a limit of NMT 0.50%, which is in line with the limit provided in the Ph. Eur. monograph of clopidogrel hydrogen sulfate.

Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Two starting materials are used. Upon request one of the starting materials was redefined during the procedure. After the redefinition of starting material the active substance manufacturing process contains three chemical transformation steps, one chiral resolution and one purification step.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The discussion on carry-over of materials from the starting material is provided in the Restricted Part of the ASMF.

The potential impurities have been identified and the origin of each impurity is stated.

Starting materials were tested in three batches of active substance with validated analytical procedures. The results show they are not detected, hence their control in the active substance specification is not needed. The same applies also for the Step I and Step II intermediates.

Genotoxic impurities have been identified. The Option 4 approach of ICH M7 is applicable for one of the genotoxic impurity. The carryover studies to active substance for two impurities show to be well below the 30% of TTC. It is acceptable to not include these impurities in the active substance specification. The results for ICH Q3D Class-1 (As. Pb, Cd, Hg) and Class-2A (Co, V, Ni) elements are provided. All results were found to be below detection limit. The information on analytical methodology used for the determination of elemental impurities is provided.

The provided information on description and control of the container closure system (HMLDPE bag inserted in triple laminated aluminium bag and outer triple laminated aluminium bag) for the active substance is considered satisfactory. Compliance of the primary packaging with EU regulation 10/2011 has been confirmed.

Specification

The active substance specification includes tests for appearance, solubility, identification (specific optical rotation, IR, enantiomeric purity, test for sulfates), appearance of solution, water content (KF), sulfated ash, enantiomeric purity (HPLC), related substances (HPLC) assay (HPLC), residual solvents (GC), identification of polymorph (XRPD) and particle size.

Specification limits are set according to the Ph. Eur. monograph for clopidogrel hydrogen sulfate and general requirements of Ph. Eur. Additional test parameters are residual solvents, identification of polymorph and particle size. The limits for residual solvents are in line with the ICH Q3C limits. The limits for particle size were added in the active substance specification in accordance with the data in the pharmaceutical development section. Stability indicating parameters are included in the stability testing. The test parameters included in the specification are adequate, and the corresponding acceptance limits are considered justified.

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

Sufficient information is provided regarding the reference standards used in the control of the active substance.

Batch analysis data for three production scale batches are provided and are in compliance with the proposed specification. The provided batch analysis data confirm consistency of the manufacturing process and the quality of the active substance.

Stability

Stability studies (ICH long term: 25°C ± 2°C / 60% ± 5% RH and accelerated: 40°C ± 2°C / 75% ± 5% RH) were carried out for three production scale batches stored in the intended commercial packaging. The following parameters were tested:

- Appearance
- Identification by IR
- Water content (%w/w, by KF)
- Enantiomeric purity (% area normalization, by HPLC); impurity C
- Related substances (% w/w, by HPLC); impurity A, impurity B, any unspecified impurity, total impurities
- Assay (%w/w on anhydrous basis, by HPLC)
- Identification of polymorph (by XRPD)

Analytical results demonstrating the stability indicating nature of the HPLC method for assay (in-house method) have been provided. Analytical methods are the same as those used for the release testing.

Storage under long-term and accelerated conditions showed no upward or downward trends, all the results remain within the specification. Based on the provided 24 months long term stability data a retest period of 3 years is considered acceptable.

A photostability study has not been performed which is accepted as the active substance is stored protected from light.

Acetylsalicylic acid

General Information

The chemical name of acetylsalicylic acid is 2-(acetyloxy)benzoic acid, corresponding to the molecular formula $C_9H_8O_4$. It has a relative molecular mass of 180.2 and the following structure (Figure 2):

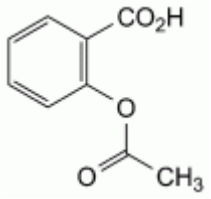

Figure 2 Acetylsalicylic acid structure

Acetylsalicylic acid is a white or almost white, crystalline powder or colourless crystals. It is slightly soluble in water and freely soluble in ethanol (96 per cent). There are no reports of polymorphic forms of acetylsalicylic acid in the literature.

As there is a monograph of acetylsalicylic acid in the European Pharmacopoeia (monograph 01/2017:0309), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for acetylsalicylic acid which has been provided within the current Marketing Authorisation Application.

Manufacture, process controls and characterisation

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The specification for acetylsalicylic acid from the finished product manufacturer includes tests for appearance, solubility, identification (IR, Melting point of precipitate, Colour test, Test for salicylates), appearance of solution, melting point, related substances (HPLC), loss on drying, sulphated ash, assay and particle size.

The specification is in line with the Ph. Eur. monograph for acetylsalicylic acid, with additional tests for particle size. The limit for particle size is in line with the studies provided in section 3.2.P.2 Pharmaceutical Development.

The related substances are sufficiently controlled by the monograph and no additional impurities are presented above the reporting threshold. Acetic acid is used as a solvent in the last steps of the synthesis. Its residual content is limited by the test for loss on drying.

The analytical methods have been adequately described.

Adequate information on reference standards have been provided.

Batch analysis data on two active substance batches have been provided.

Stability

Stability studies under ICH long term at 25°C ± 2°C / 60% ± 5% RH and accelerated at 40°C ± 2°C & 75% ± 5% RH conditions were carried out on three production scale batches. Samples were stored in a double polythene bag kept in HDPE drum or in a polythene bag kept in kraft paper bag.

The following parameters were tested: description, loss on drying, related substances and assay.

Based on the stability data provided (36 month long term and 6 month accelerated), the claimed re-test period of 3 years with no specific storage conditions is regarded justified. The proposed re-test period is accepted for both container closure systems stated on the CEP (double polyethylene bags placed in a polyethylene or fibre drum or alternatively in a polyethylene bag placed in a polyethylene laminated paper bag.).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition

The finished product is formulated as fixed dose combination immediate release film coated tablets in two strengths (75/75 mg and 75/100 mg). Both strengths of clopidogrel (as hydrogen sulphate) and acetylsalicylic acid tablets are dose proportional. Other ingredients are:

- **Tablet core**: cellulose microcrystalline, lactose, croscarmellose sodium, hydroxypropylcellulose, colloidal anhydrous silica, talc, hydrogenated castor oil, pregelatinized starch, stearic acid, iron oxide yellow (E172)
- **Coating for 75 mg/75 mg film-coated tablets**: hypromellose, triacetin, talc, poly (vinyl alcohol) (partially hydrolysed), titanium dioxide, iron oxide yellow (E172), glycerol monocaprylocaprate Type 1, sodium lauril sulfate
- **Coating for 75 mg/100 mg film-coated tablets**: hypromellose, triacetin, talc, poly (vinyl alcohol) (partially hydrolysed), titanium dioxide, allura red AC (E129), glycerol monocaprylocaprate type 1, sodium lauril sulfate

According to the SmPC dosing of the applied product should be given as a single daily 75 mg/75 mg or 75 mg/100 mg dose.

Clopidogrel and acetylsalicylic acid 75mg/75mg film-coated tablets are yellow, oval shaped, biconvex, film-coated tablets, debossed with "CA2" on one side of the tablet and "M" on the other side. Dimensions: Approximately 14.5 mm × 7.4 mm

Clopidogrel and Acetylsalicylic Acid 75mg/100mg film-coated tablets are pink, oval shaped, biconvex, film-coated tablets, debossed with "CA3" on one side of the tablet and "M" on the other side. Dimensions: Approximately 14.8 mm × 7.8 mm

The Opadry used in the seal coating and film-coating are purchased from the supplier as a fully-formulated material; therefore, finished product manufacturer does not test and release the individual ingredients.

Container/Closure

The product is presented in the following pack types:

- Aluminium blisters with desiccant layer containing 28 or 30 film-coated tablets.
- Aluminium perforated unit dose blisters with desiccant layer containing 28 or 30 film-coated tablets.
- HDPE bottles with white opaque polypropylene screw cap with aluminium induction sealing liner wad and desiccant containing 100 film-coated tablets.

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. The provided information on description and control of the container closure system is considered satisfactory.

Pharmaceutical development

The purpose of the pharmaceutical development studies was to develop an essentially similar, generic version of the branded formulation. The reference product DuoPlavin (clopidogrel and acetylsalicylic acid 75mg/75mg and 75/100 mg film-coated tablets), Sanofi Pharma Bristol-Myers Squibb SNC and the Applicant's clopidogrel and acetylsalicylic acid 75mg/75mg and 75mg/100mg film-coated tablets are essentially similar and contain the same active ingredients i.e. clopidogrel hydrogen sulfate (Ph. Eur.) and acetylsalicylic acid (Ph. Eur).

The quality target product profile (QTPP) was defined as immediate release tablets to be administered orally, containing 75/74 mg and 75/100 mg of clopidogrel (as hydrogen sulfate) (Ph. Eur.) and acetylsalicylic acid (Ph. Eur.) as active ingredients and be pharmaceutically equivalent to the reference product. Further, the product should have satisfactory pharmaceutical stability and a comparable dissolution profile to the reference product.

The critical quality attributes defined were identification, assay, content uniformity, related substances, dissolution and microbiological test.

During product development, all attributes in the QTPP were monitored. Risks assessments were performed to identify the formulation variables and process parameters affecting the identified critical quality attributes (CQAs).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards, except Opadry clear, Opadry yellow and Opadry pink which are premixtures, but their components comply with Ph. Eur, where available. Iron oxide yellow (E172) FD&C Red #40/ Allura red AC Aluminium Lake (E129) are not described in Ph. Eur. but they comply with Commission Regulation (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Based on the reference product it was decided to develop a bilayer tablet formulation in which clopidogrel hydrogen sulfate is included in one layer and acetylsalicylic acid in another layer.

The qualitative composition of the excipients is different from that of the reference product. The excipients mannitol and macrogol 6000 are not present in the proposed formulation. Instead, lactose (diluent) has been chosen in the proposed formulation after the trial development studies. Moreover, the film-coating system used is different from that of the reference product. The justification for the differences in the composition

versus the reference product has been supported with experimental dissolution data and drug-excipient compatibility studies.

A risk assessment of the active substances attributes was performed to evaluate the impact that each attribute could have on the finished product CQAs.

Information about active substance and excipients is considered acceptable. The formulation development has been described in detail.

To select the dissolution conditions for routine quality control testing, the dissolution behavior was studied on test product Clopidogrel and Acetylsalicylic acid Tablets in various dissolution media in volume of 900 ml using dissolution apparatus II. Considering the results of studied media and literature information a common dissolution release medium for both clopidogrel and acetylsalicylic acid was selected.

The discriminatory power of the test conditions has been demonstrated by dissolution studies on different batches formulated with slightly modified process and composition.

The absorption kinetics of clopidogrel and acetylsalicylic acid is linear within the therapeutic range.

The results of *in vitro* dissolution tests in three different buffers (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) and the media intended for finished product release, obtained with the test (1 batch 75/75 mg and one batch 75/100 mg, the latter was used in the bioequivalence study) and reference product (1 batch 75/100 mg, used in the bioequivalence study) batches have been provided using dissolution apparatus Type – II (Paddle), in 900 mL, temperature: 37°C ± 0.5°C.

Similarity factors were calculated between the pivotal bio-batch and the reference product. Test and reference product showed similar dissolution profiles in several media. However, dissolution profiles are not comparable for acetylsalicylic acid in pH 2.0 and for clopidogrel in pH 4.5. The applicant has addressed the reasons for the discrepancy, explaining that the test product has slower dissolution at the initial time point as its coating system may take longer duration to dissolve as compared to the reference product

The bioequivalence study was carried out on the highest strength (75/100 mg). One multidisciplinary major objection was raised in relation to selection of the agitation speed for the dissolution method used for QC testing and to support a biowaiver for the lower strength.

To support the proposed agitation speed for the QC testing the applicant demonstrated that study results generated at agitation speed of 50 rpm showed incomplete drug release after 45 min and higher variability in the earlier time points for both clopidogrel and acetylsalicylic acid. Less variability and complete release was observed for clopidogrel and acetylsalicylic acid at the proposed agitation speed. With regard to the biowaiver of strength the applicant provided additional dissolution profiles of the bio-strength (75/100 mg) and lower strength (75/75 mg) using the agitation speed of 50 rpm as requested. Bootstrapping was performed for calculation of similarity factors where the RSD value is found to be too high at the early time points. The results provide reassurance that the release profile of the bio-batch (75/100 mg) is similar to the release profile of the lower strength (75/75 mg).

As apparent from the results of the comparative impurity profile study, both test product and the reference product exhibit similar impurity profile.

The manufacturing process was optimized for roller speed and roller force, precompaction blending, compaction, milling, post-compaction blending for clopidogrel part and blending for acetylsalicylic acid, tablet hardness range and coating build-up.

Manufacture of the product and process controls

There is one manufacturer of the finished product. The critical steps involved in the finished product manufacturing process include blending, compression, coating and packaging. The process is considered to be a standard manufacturing process.

The in-process controls are sufficiently described and the frequency of testing is suitable.

The manufacturing process has been validated at the smaller production scale.

Product specification, analytical procedures, batch analysis

The finished product release specification include appropriate tests for this kind of dosage form: description, identification (HPLC), colour identification, dissolution (HPLC), uniformity of dosage units, assay (HPLC), water (KF), microbiological test, residual solvents (GC), related substances (HPLC) and enantiomeric purity (HPLC).

Overall, the finished product specifications have been adequately set in accordance with ICH Q6A and Ph. Eur. and the justifications provided are acceptable. The identified impurities are in line with the impurities listed for the active substance, no new impurities are expected for the finished product.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the data presented it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Analytical methods and reference standards

The analytical methods used for the control of the finished product have been satisfactorily described and validation data of the in-house analytical methods are in accordance with the requirements of the relevant ICH guidelines. Satisfactory information regarding the reference standards used for assay and related substances testing has been presented.

Batch analysis

Batch analysis results for three commercial size batches of each strength have been provided. The results confirm consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of each strength stored for up to 12 months under long term conditions (25 ± 2°C/60 ± 5% RH) and intermediate conditions (30 ± 2°C/75 ± 5% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packagings proposed for marketing (i.e. desiccant cold form blister pack and HDPE bottle pack)

Samples were tested for: description, assay, dissolution, water by KF, enantiomeric purity, related substances and microbiological test. The analytical procedures used are stability indicating. The data indicate a slight increase in impurities over time, but all results were within the shelf-life specification.

The Applicant also provided up to 6 months stability data at accelerated storage condition (40°C ± 2°C/75% RH ± 5% RH). Results for impurities and dissolution were out of specification.

The shelf life initially claimed by the applicant was not accepted and a major objection was raised on the lack of appropriate data to support this proposal. Although 12 months stability data at both intermediate and long-term storage conditions for the proposed pack types are provided and found acceptable, the shelf-life could be extended for a maximum 3 months (i.e. a shelf life of 15 months) in view of the significant changes observed at the accelerated storage condition. In response, the applicant reduced the shelf-life to 15 months which was considered acceptable.

Forced degradation studies were performed during validation of the assay and related substances test methods. It was concluded that the degradation studies conducted are indicative enough to understand the degradation nature of the molecules and its impact on the method capability to quantify the degradants. Moreover, peak purity data established for these forced degradation studies indicate that no degradants will coelute with clopidogrel or acetylsalicylic acid peaks.

Photostability was studied as per ICH Q1B. The study results indicated that clopidogrel and acetylsalicylic acid 75mg/100mg film-coated tablets are photostable as there were no out of specification results.

In-use stability results for two bottle batches per strength were performed. The results were in compliance with the specification and based on the data provided, it is not considered necessary to establish an in-use shelf life.

Based on the available stability data, the proposed shelf-life of 15 months when stored at up to 25°C as stated in the SmPC (section 6.3) is considered acceptable.

Adventitious agents

It is confirmed that the lactose used 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. This is considered satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological 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 indicated 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.

During the procedure one major objection was raised for one of the proposed starting materials for clopidogrel hydrogen sulfate. The starting material was redefined, and the new starting material was accepted. Another major objection related to lack of sufficient data to support the proposed shelf life of the finished product. The initially proposed shelf life was therefore reduced to 15 months, which is considered acceptable. A multidisciplinary major objection was raised regarding the dissolution method used for QC testing and to support the biowaiver of strengths as the applicant was using a selected agitation speed o and not 50 rpm. Further data and justifications were provided to satisfactorily justify the use of the selected agitation speed for the QC testing (insufficient drug release at 50 rpm) and provide reassurance that the

release profile of the bio-batch (75/100 mg) was similar to the release profile of the lower strength (75/75 mg).

2.2.5. Conclusions on 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.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. The justification initially submitted by the Applicant for not providing new ERA studies was not considered adequate. In line with the Questions and answers on Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the Applicant was requested during the procedure to justify the absence of a possible significant increase of environmental exposure to the drug substances, providing concrete relevant data such the consumed quantities of active substances in kg/year, and based on European disease prevalence data for the refinement of Fpen. Furthermore, the Applicant was requested to provide information on an experimentally derived n-octanol/water partition coefficient (log Kow) for acetylsalicylic acid and clopidogrel. The Applicant provided the requested revised justification which was considered acceptable by the CHMP. The introduction of Clopidogrel/Acetylsalicylic acid Mylan manufactured by Mylan S.A.S is considered unlikely to result in any significant increase in the combined sales volumes for all clopidogrel / acetylsalicylic acid containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamics, pharmacokinetic and toxicological properties of clopidogrel and acetylsalicylic acid are well characterised as both active substances are widely used and well-known. It is agreed that no further non-clinical studies are required. A non-clinical overview provided by the applicant covers recent available literature concerning the non-clinical pharmacology and toxicology of clopidogrel hydrogen sulphate and acetylsalicylic acid and is considered appropriate.

Based on the Phase II ERA studies of clopidogrel and acetylsalicylic acid conducted by Sanofi-Aventis and Bayer Bitterfeld GmbH, respectively, the justification for non-submission of an Environmental Risk Assessment provided by the Applicant is considered acceptable.

The impurity profile of Clopidogrel/acetylsalicylic acid Mylan film-coated tablets 75 mg/75 mg and 75 mg/100 mg was compared with European reference product DuoPlavin 75 mg/75 mg and 75 mg/100 mg film-coated tablets marketed by Sanofi Pharma Bristol-Myers Squibb SNC. No additional impurities were observed in the test product. Products are considered as essentially similar from aspect of the impurity profile.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.4. Conclusion on the non-clinical aspects

Pharmacodynamics, pharmacokinetic and toxicological properties of clopidogrel and acetylsalicylic acid are well characterised as both active substances are widely used and well-known. It is agreed that no further non-clinical studies are required. No Environmental Risk Assessment studies were submitted which is considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing clopidogrel and acetylsalicylic acid. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), Question number 4.1 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604) and the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017) in their current version are of particular relevance.

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.

Exemption

Justification for Biowaiver (for 75 mg/75 mg strength)

The Applicant requested a biowaiver for the 75 mg/75 mg strength, based on the result of the bioequivalence study conducted with the 75 mg/100 mg mg strength, with the following justification provided:

- Both strengths of clopidogrel and acetylsalicylic acid film-coated tablets (75 mg/75 mg mg and 75 mg/100 mg) are manufactured by the same manufacturer at the same manufacturing site and manufacturing process.
- Linear pharmacokinetics, i.e. proportional increase in AUC and C_{max} with increased dose, over the therapeutic dose range.
- The qualitative composition of both strengths is the same.
- The composition of both strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substances is the same for both strengths (except for coating components, color agents and flavors).
- Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

➢ **Linear pharmacokinetics of ASA**

Linear pharmacokinetics of ASA over the dose range of 30 mg to 100 mg have been published (Dubovská et al., 1995) which gives evidence for the extrapolatability of the results of clopidogrel and acetylsalicylic acid film-coated tablets 75 mg/100 mg to the other tablet strength 75 mg/75 mg of this application also from the pharmacokinetic point of view.

➢ **In-vitro Dissolution Data for Biowaiver Request for Different Strengths**

The experimental dissolution conditions are as follows:

Parameter	*Conditions*
Dissolution media:	Release media

0.1N Hydrochloric acid
pH 4.5 Acetate buffer
pH 6.8 Phosphate buffer

Dissolution apparatus: Type – II (Paddle with sinker)
Volume: 900 mL
Temperature: 37°C ± 0.5°C
Sampling time (for profile study only): 10 min, 15 min, 20 min, 30 min and 45 min

Test product used in the bioequivalence study vs other strength of Test product vs Reference product

The dissolution profile data was generated for test batches of clopidogrel and acetylsalicylic acid tablets 75 mg/75 mg and 75 mg/100 mg in different pH conditions like 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and release media. The summaries of comparative dissolution profiles between biobatch and the lower strength batch and European reference product in different media are provided in the application.

The similarity factor (f2 value) was calculated between bio-batch and lower strength batch. The bootstrap calculation method is used for calculation of similarity factor as higher relative standard deviation (RSD) was observed in one buffer for one of the drug component. The summaries of f2 value comparison between biobatch and lower strength batch in different media are provided.

Based on the above data of f2 values, it can be concluded that both batches express similar dissolution profile for both Clopidogrel and Acetylsalicylic acid across the pH range of 1.2 to 6.8.

The dissolution methodology and the dissolution profile similarity testing followed the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010).

During the evaluation procedure, the Applicant was requested to justify the selection agitation speed. In order to justify the selection of agitation speed for this product instead of 50rpm, the Applicant provided during the evaluation new comparative dissolution study results between the lower strength (75/75 mg) and bio-strength (75/100 mg) of the test product at rotation speed of 50 rpm in QC release media . The dissolution study results generated at agitation speed of 50 rpm showed incomplete drug release after 45 min and higher % RSD in the earlier time points for both clopidogrel and acetylsalicylic acid. Whereas less variability and complete release was observed for clopidogrel and acetylsalicylic acid at selected agitation speed.

Moreover, the Applicant has performed comparative dissolution profiles of bio-strength (75/100 mg) and lower strength (75/75 mg) in physiological pH range (0.1N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and in QC media) using the agitation speed of **50 rpm** as requested. The similarity factor (f2 value) were calculated between bio-strength and lower strength batch.

After assessment of the applicant's response, it was concluded that the selected agitation speed for *in vitro* dissolution tests to support a biowaiver of lower strength 75 mg/75 mg has not been adequately justified. Calculation of f2-values in the case above is not allowed as the RSD values at the early time points were too high. Therefore, the Applicant was requesting to perform bootstrapping. When the $f2$ statistic is not suitable due to too high RSD values, then the 90% confidence interval of the f2 similarity factor calculated by bootstrapping is recommended. Similarity between two dissolution profiles can be concluded when the lower limit of the 90% CI of f2 is equal or greater than 50. A description of the software used and output of the software should be included.

To answer the question raised regarding the selection of agitation speed for this product, the Applicant performed the bootstrapping for calculation of similarity factor for the dissolution profiles at agitation speed of 50 rpm where the RSD value is found to be higher at the early time points. The summary of bootstrap analysis and similarity factor calculation for dissolution profiles at agitation speed of 50 rpm in different mediums showed that f2 was more than 50 but lower limit (5th percentile) of the 90% CI of f2 is observed to be slightly less than 50 for some of the dissolution profiles of clopidogrel and acetylsalicylic acid.

Furthermore, the Applicant provided the requested photographs for visual observation of dissolution of Clopidogrel and Acetylsalicylic acid tablets 75/75mg and 75/100 mg at both 50 & selected rpm. The presented photographs show unstirred contents (coning) at bottom of dissolution vessel at 50 rpm whereas less unstirred contents is observed at selected rpm after 20 min, 30 min and 45 min. Thus, the selection of agitation speed for *in vitro* dissolution tests is considered appropriate by the CHMP.

In order to justify the exclusion of the first sampling time point , the Applicant provided during the evaluation results of disintegration time observed at compression stage (un-coated) of clopidogrel and acetylsalicylic acid tablets. The above data indicates that core tablets of both strengths are having a longer disintegration time. Taking into consideration that clopidogrel and acetylsalicylic acid tablet is a bilayer tablet which consists of two separate layers of clopidogrel and acetylsalicylic acid and having a longer disintegration time and the higher variability in dissolving of film coating layers in earlier time points of dissolution profile study will not have any impact on *in vivo* performance of clopidogrel and acetylsalicylic acid, the exclusion of the first sampling point is considered justified.

Furthermore, the Applicant performed during the evaluation the dissolution profile study for two other pilot scale batches of clopidogrel and acetylsalicylic acid tablets 75/75 mg and clopidogrel and acetylsalicylic acid tablets 75/100 mg . The dissolution profile results are provided.

The similarity factor (f2 value) has been calculated between bio-batch and other two pilot scale batches of 75/100 mg and other two pilot scale batches of lower strength 75/75 mg . The bootstrap calculation method is used for calculation of similarity factor as higher %RSD was observed for one of the drug component. The summaries of f2 value comparison are provided below.

Comparison of dissolution profiles shows that the above batches of both strengths express similar dissolution profiles to that of bio batch (BEQ) for both active substances. However, the 90% confidence interval of the f2 obtained from the bootstrap method was not initially reported in the submitted documentation. The Applicant provided during the procedure the requested similarity factor calculation including 90% confidence interval for bootstrap statistical evaluation of dissolution profiles for clopidogrel.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The Applicant committed to perform comparative dissolution profile on the production scale batches of clopidogrel and acetylsalicylic Acid 75mg/75mg and 75mg/100mg film-coated tablets. The results will be provided at a Competent Authority's request or if the dissolution profiles are not similar together with proposed action.

B) Comparative dissolution studies (Test product versus reference product)

The Applicant carried out comparative dissolution studies, using the selected rotation speed , between the EU reference product DuoPlavin 75 mg/100 mg tablets and the test product clopidogrel and acetylsalicylic acid 75 mg/100 mg (both used in BE study) in different dissolution media i.e. 0.1N HCl, , pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and Release media covering the pH range of pH 1.2 to pH 6.8.

Similarity factor (f2 value) was calculated between pivotal biobatch and EU reference product DuoPlavin Tablets 75/100 mg tested in release media, 0.1N HCl and pH 4.5 (at the selected rotation speed) was calculated using the multiple sampling time points excluding the first sampling time point , without providing appropriate justification for this selective approach. The bootstrap calculation method is used for calculation of similarity factor as higher RSD was observed in one media for one of the drug component.

The summaries of f2 value comparison between pivotal biobatch and reference product for Clopidogrel hydrogen sulfate and Acetylsalicylic acid are provided.

The above comparison of f2 value indicates that the clopidogrel and acetylsalicylic acid tablets 75/100 mg and DuoPlavin Tablets 75/100 mg are having the similar dissolution profiles for clopidogrel in 0.1 N HCl, release media and pH 6.8 and for acetylsalicylic acid in 0.1 N HCl, pH 4.5 and pH 6.8. However, dissolution profiles are not comparable for acetylsalicylic acid in one media and for clopidogrel in one media . The Applicant addressed the reasons for the discrepancy. The Applicant argued conclusively that the test product has slower dissolution at initial time point as it consists of two film coating process i.e. seal coating and moisture barrier coating which may take longer duration to dissolve as compared to the reference product where in hypromellose based coating is present. In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo, the latter prevails.

Clinical studies

To support the application, the Applicant submitted one bioequivalence study, Bioequivalence study No.: C18156 under fasting conditions.

Table 1 Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	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
BA	Not Applicable								
BE	Project No. C18156	Clinical Study Report & PK Report and Adverse Event Listing **Clinical Study (5.3.1.2)** Bioanalytical Report **Bioanalytical (5.3.1.4)** CRFs and Individual Subjects **Individual CRF (5.3.7)** Literature References **Literature References (5.4)**	**Primary objective:** Primary Objective was to evaluate the oral bioequivalence of Clopidogrel bisulfate and Aspirin Tablets 75mg / l00mg of Mylan Laboratories Limited, India with DuoPlavin (Clopidogrel Hydrogen sulphate and Acetyl salicylic acid) 75mg/100mg film coated tablets of Sanofi Winthrop Industrie1, rue de la Vierge, Ambarès & Lagrave, F-33565 Carbon Blanc cedex, France, in normal healthy adult human subjects under fasting conditions. **Secondary objective:** Secondary Objective was to monitor the adverse events and to ensure the safety of the subjects	A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal healthy adult human subjects under fasting conditions.	Test Drug (A): Clopidogrel and acetylsalicylic acid tablets 75mg/100mg, 1 x 75mg/100mg, oral. Reference Drug (B): DuoPlavin® 75mg/100mg filmtabletten Clopidogrel/acetylsalicylsaure, 1 x 75mg/100mg, oral.	Planned - 76 subjects+ A maximum of 04 additional subjects (2 additional subjects per each group) Enrolled - Group-I: 32 subjects (subject numbers 01-32)+02 additional subjects (standby-I &standby-II) Group-II: 44 subjects (subject numbers 33-76) +02 additional subjects (standby-III &standby-IV) Dosed: Group-I: Period-1: 32 subjects Period-2: 32 subjects Group-II Period-1: 44 subjects Period-2: 42 subjects Completed - 74 subjects Withdrawn: 02 subjects (subject numbers 46 & 67) Bio-sample analyzed – 74 subjects Pharmacokinetic and statistical data analyzed – 74 subjects.	Healthy, adult, human male subjects	Single-dose	Complete; Abbreviated
PK	Not Applicable								
PD	Not Applicable								
Efficacy	Not Applicable								

2.4.2. Pharmacokinetics

Study C18156: A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Clopidogrel bisulfate and Aspirin Tablets 75mg / l00mg of Mylan Laboratories Limited with DuoPlavin (Clopidogrel Hydrogen sulphate and Acetyl salicylic acid) 75mg/100mg film coated tablets of Sanofi Winthrop, in normal healthy adult human subjects under fasting conditions.

Methods

Study design

This was a randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study to compare the bioavailability of 2 formulations of clopidogrel, clopidogrel carboxylic acid and ASA (75 mg/100 mg) under fasting conditions.

Table 2 Summary of study information

Study Site (clinical, bioanalytical, statistical):	Aizant Drug Research Solutions Pvt. Ltd., Survey No.: 172 & 173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India-500100
Sponsor:	Mylan S.A.S., India
Principal investigator:	Dr. Bala Krishna. N, M.B.B.S, M.D
Clinical Phase Dates:	Group-I: 04. Jun 2018 – 15. Jun 2018 Group-II: 13. Jun 2018 – 22. Jun 2018
Date of the Clinical Study Report:	29 August 2018
Bioanalytical Phase Dates:	Aspirin & Salicilic acid: 30 June 2018 to 20 July 2018 Clopidogrel: 02 July to 26 July 2018 Clopidogrel carboxylic acid: 29 June to 16 July 2018
Date of the Bioanalytical Phase Report:	22 August 2018
Date of the Method Validation Report	Clopidogrel: 21 November 2017 Latest Addendum (03): dated on 22 August 2018 ASA & Salicilic acid: 27 June 2018 Clopidogrel carboxylic acid: 06 February 2018

The study was conducted at the highest/most sensitive strength and under fasting conditions, which reflects recommendations in the reference product's summary of product characteristics for the administration of the product irrespective of mealtimes and it is considered to be the most sensitive condition to detect a potential difference between formulations. The measurement of the parent compound (clopidogrel and ASA) is also according to Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor.).

The study was conducted on 76 healthy, adult, human subjects in accordance with the protocol. 74 subjects completed the study. The study was conducted in two groups and in each group, the subjects received one tablet of either test or reference product randomly with 240 mL of ambient temperature on the day of dosing as per the randomization schedule under fasting conditions in each period of the study. The drug product was administered after at least 10.00 hours overnight fasting. Drug administration carried out at 02-minute intervals. A 9 days washout separated each period in group-I and 7 days washout separated each period in group-II.

Blood samples were collected at pre-dose (0.00 hours) and at intervals over 24.00 hours after administration of dose. The sampling period was sufficient to characterize the plasma concentration-time profile. Blood sampling points are appropriate to allow an accurate measurement of T_{max}.

Given a half-life of clopidogrel of 6 hours and a half-life of clopidogrel carboxylic acid of 8 hours, the sampling period and wash-out period of 9 days (group I) and 7 days (group II) were long enough (more than 5 times of the elimination half-lives of the substances) to avoid any carry-over effect. Given a half-life of acetylsalicylic acid (ASA) of 15-30 minutes and a half-life of salicylic acid (SA) of 2-3 hours, the sampling period and wash-out period of 9 days (group I) and 7 days (group II) were long enough (more than 5 times of the elimination half-lives of the substances) to avoid any carry-over effect. The absorption process was likely covered with the given sampling schedule.

The Applicant made changes in the study protocol regarding the name of the test and reference products and the reference product manufacturer address. Those changes were not approved by the Independent Ethics Committee and this was raised as a GCP issue. During the procedure, suitable explanation why the protocol was changed without the approval of Independent Ethics Committee was provided by the Applicant and this was considered satisfactory by the CHMP.

No other protocol deviations have been registered other than minor deviations from the blood sampling time points and dispensing time of investigational products. The deviation in dispensing time of investigational products is not considered significant and had no impact on study results. The deviations in scheduled sampling time had no impact on study results as actual sampling times were used for PK calculations.

Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Clopidogrel and acetylsalicylic acid tablets 75mg/100mg	DuoPlavin® 75mg/100mg filmtabletten Clopidogrel/acetylsalicylic acid)
Strength	75mg/100mg	75mg/100mg
Dosage Form	Tablets	Tablets
Batch number/ Lot number	2014503	7A220
Batch Size (Biobatch)	240000	Not available
Measured Content(s) (% of Label Claim)	Clopidogrel: 103.4 % w/w Acetylsalicylic acid: 100.8 % w/w	Clopidogrel: 103.4 % w/w Acetylsalicylic acid: 101.7 % w/w
Commercial Batch Size	Not applicable	Not available
Expiry Date	Dec 2019.	05/2019
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.7	5312-compar-ba-be-stud-rep, Appendix-16.1.7
Member State where the reference product is purchased from:	Not applicable	EU
This product was used in the following trials:	Study no.: C18156	Study no.: C18156

Clopidogrel/Acetylsalicylic acid Mylan 75/100 mg manufactured by Mylan Laboratories Limited (batch No. 2014503,; exp. Date: December 2019) has been compared to DuoPlavin 75/100 mg manufactured by Sanofi Clir SNC (Batch No: 7A220, exp. Date: May 2019).

The reference and test products were considered acceptable by the CHMP.

During the procedure. a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation was provided by the Applicant.

Population(s) studied

The study was conducted in two groups. In Group-I 32 plus 2 additional subjects (standby-I & II) and in Group-II 44 plus 2 additional subjects (standby-III & IV) healthy volunteers human subjects meeting the inclusion and exclusion criteria as mentioned in the study protocol were enrolled in to the study to ensure the dosing of 76 subjects. All the dosed subjects (32 subjects) in Group-I completed the clinical phase of the study successfully. From Group II, 2 subjects withdrawn (subject number 46 & 67) prior dosing in period 2 and in all, 42 subjects in Group-II completed the clinical phase of the study successfully. A total of 74 subjects were included in pharmacokinetic and statistical analysis.

The population chosen was according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria were acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization. The reason of the withdrawal was acceptable. During the procedure, the Applicant provided adequate justification for not providing the concentration data of withdrawn subjects from the study. The Case report forms of subject's no.46 and 67 participated in the study were provided as requested. This was considered acceptable by the CHMP.

Analytical methods

Acetyl salicylic acid and salicylic acid:

The plasma samples of subjects were analyzed for acetyl salicylic acid and salicylic acid in human sodium fluoride and potassium oxalate plasma using validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method over a concentration range of 15.787 - 4049.961 ng/mL for analyte and 78.891 - 20238.774 ng/mL for metabolite [BL-MV-315 Version-00]. The performance of the bioanalytical method was verified by bioanalytical laboratory of Aizant Drug Research Solutions Pvt. Ltd.

Table 3 Study sample information

First sample collection date	05 Jun 2018	
Number of subjects (as per protocol)	76	
Number of periods (as per protocol)	2	
Subject sample analysis started on	30 Jun 2018	
Total No. of subjects samples processed	3698	
Date of repeat analysis	07 Jul 2018	
Total No. of samples subjected for repeat analysis	Analyte	51*
	Metabolite	78*
No. of samples accepted after repeated analysis	Analyte	51*
	Metabolite	78*
Analysis completed on	20 Jul 2018	
Total analysis time	21 Days	
Storage duration of project samples (Difference between the first sample collection date to last sample analysis date)	46 Days	
Long term stability proved at -28 ± 5°C and -70 ± 15°C	54 Days (Performed in Addendum 01)	

** Individual Repeats*

Table 4 ISR (Incurred samples reanalysis) for ASA

Analyte	Acetyl salicylic acid
Total numbers of collected samples	3748
Total number of samples with valid results	3698
Total number of reassayed samples[1,2]	51
Total number of analytical runs[1]	77
Total number of valid analytical runs[1]	76
Incurred sample reanalysis	
Number of samples	372
Percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays	95.43 %

[1] Without incurred samples and BSC

[2] Due to other reasons than not valid run

Results of the performed ISR experiment met the acceptance criteria, as 95.43% of the 372 incurred samples were within the acceptance range for ASA.

Table 5 ISR (Incurred samples reanalysis) for Salicylic acid

Metabolite	Salicylic acid
Total numbers of collected samples	3748
Total number of samples with valid results	3698
Total number of reassayed samples[1,2]	78
Total number of analytical runs[1]	80
Total number of valid analytical runs[1]	76
Incurred sample reanalysis	
Number of samples	372
Percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays	94.89 %

[1] Without incurred samples and BSC

[2] Due to other reasons than not valid run

Results of the performed ISR experiment met the acceptance criteria, as 94.89% of the 372 incurred samples were within the acceptance range for Salicylic acid.

The analytical method was validated, either pre-study and within study, however not entirely conducted according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009. After assessment of the Applicant's responses, it is concluded that the bioanalytical method was satisfactorily validated, either pre-study and within study. Handling of samples was adequate. Reasons for reanalysis of samples are considered acceptable. Incurred sample reproducibility tests were acceptable.

Clopidogrel:

The plasma samples of subjects were analyzed for clopidogrel in human K_3 Ethylenediaminetetraacetic acid (EDTA) plasma using validated LC/MS/MS method over a concentration range of 10.007 - 4013.922 pg/mL [BL-MV-281 Version-00]. The performance of the bioanalytical method was verified by bioanalytical laboratory of Aizant Drug Research Solutions Pvt. Ltd.

Table 6 Study sample information

First sample collection date	05 Jun 2018	
Number of subjects (as per protocol)	76	
Number of periods (as per protocol)	2	
Subject sample analysis started on	30 Jun 2018	
Total No. of subjects samples processed	3698	
Date of repeat analysis	07 Jul 2018	
Total No. of samples subjected for repeat analysis	Analyte	51*
	Metabolite	78*
No. of samples accepted after repeated analysis	Analyte	51*
	Metabolite	78*
Analysis completed on	20 Jul 2018	
Total analysis time	21 Days	
Storage duration of project samples (Difference between the first sample collection date to last sample analysis date)	46 Days	
Long term stability proved at -28 ± 5°C and -70 ± 15°C	54 Days (Performed in Addendum 01)	

** Individual Repeats*

The analytical method was validated, either pre-study and within study, however not entirely conducted according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009. Handling of samples was adequate. Reasons for reanalysis of samples are considered acceptable. Incurred sample reproducibility tests were considered acceptable.

During the evaluation, the Applicant was requested to demonstrate the lack of occurrence of a potential back-conversion of clopidogrel carboxylic acid metabolite to the parent-drug (unchanged clopidogrel). The Applicant acknowledged the CHMP's observation and clarified that the potential possible back conversion of major metabolite Clopidogrel carboxylic acid to the parent-drug Clopidogrel has been extensively tested under the conditions for plasma handling and storage that occurred during the clinical and bioanalysis phases and the method was fully validated to demonstrate no back-conversion occurred. It is known that the plasma levels of clopidogrel carboxylic acid (Metabolite) can be considerably higher than those of the parent clopidogrel drug, and that back conversion can occur in the presence of methanol, it is imperative that no back conversion of the carboxylic acid metabolite to the parent clopidogrel occurs. If back-conversion of the metabolite occurs, this could lead to a significant over-estimation of clopidogrel plasma levels and bias the outcome of the bioequivalence study. Since the back-conversion occurs in the presence of alcohol (methanol), no methanol or alcohol was used in any of the sample processing and extraction steps during the bioanalysis.

To demonstrate no back-conversion, multiple experiments were undertaken to demonstrate that no back-conversion occurs during the conduct of the sample collection through the bioanalysis. The major experiments needed to cover the clinical and bioanalytical phases are:

- Whole blood sample exposure (Whole blood stability)
- Plasma exposure at room temperature (Bench top stability)

- Freeze thaw cycles (Freeze thaw stability)
- Long term plasma storage stability
- Processed/Autosampler stability
- Accuracy and Precision

The experimental data obtained and presented by the Applicant during the evaluation demonstrated that samples of clopidogrel spiked with therapeutically relevant concentrations of the clopidogrel carboxylic acid do not undergo back-conversion to the metabolite to the parent compound. This was demonstrated for all conditions that occurred throughout the sample collection, processing, analysis and storage. Thus, there is no impact on the reported concentrations for the study and the reported concentrations are valid, reliable and reproducible.

Clopidogrel carboxylic acid:

The plasma samples of subjects were analyzed for clopidogrel carboxylic acid in human K_3EDTA plasma using validated LC/MS/MS method over a concentration range of 20.079 - 7999.508 ng/mL [BL-MV-284 Version-00]. The performance of the bioanalytical method was verified by bioanalytical laboratory of Aizant Drug Research Solutions Pvt. Ltd.

Table 7 Study sample information

First sample collection date	05 Jun 2018
Number of subjects (as per protocol)	76
Number of periods (as per protocol)	2
Subject sample analysis started on	02 Jul 2018
Total No. of subjects samples processed	3698
Date of repeat analysis	20 Jul 2018
Total No. of samples subjected for repeat analysis	208*
No. of samples accepted after repeated analysis	208*
Analysis completed on	26 Jul 2018
Total analysis time	25 Days
Storage duration of project samples (Difference between the first sample collection date to last sample analysis date)	52 Days
Long term stability proved at -28 ± 5°C and -70 ± 15°C	58 Days (Performed in Addendum 03)

** Individual Repeats*

The analytical method was validated, either pre-study and within study, however not entirely conducted according to Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009. After assessment of the Applicant's responses, it is concluded that the bioanalytical method was satisfactorily validated, either pre-study and within study. Handling of samples was adequate. Reasons for reanalysis of samples are acceptable. Incurred sample reproducibility tests were acceptable.

Pharmacokinetic variables

The following pharmacokinetic parameters were determined from the time and concentration data:

Clopidogrel: C_{max}, AUC_{0-t}, T_{max}, $t_{1/2}$, K_{el}, AUC_{0-inf} and (AUC_{0-t} / AUC_{0-inf}) x 100

Acetylsalicylic acid: C_{max}, AUC_{0-t}, T_{max}, $t_{1/2}$, K_{el}, AUC_{0-inf} and (AUC_{0-t} / AUC_{0-inf}) x 100

Salicylic acid: C_{max}, AUC_{0-t}, T_{max}, $t_{1/2}$, K_{el}, AUC_{0-inf} and (AUC_{0-t} / AUC_{0-inf}) x 100

Clopidogrel carboxylic acid: Cmax, AUC0-t, Tmax, t1/2, Kel, AUC0-inf and (AUC0-t / AUC 0-inf) x 100

Primary pharmacokinetic variables for assessment of bioequivalence were:

C_{max} and AUC_{0-t}

Secondary pharmacokinetic variables:

T_{max}, $t_{1/2}$, K_{el}, AUC_{0-inf} and (AUC_{0-t} / AUC $_{0-inf}$) x 100

For pharmacokinetic and statistical analysis actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using noncompartmental model of Phoenix® WinNonlin® version 8.0.

All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations.

Statistical methods

Statistical analysis was performed on ln-transformed pharmacokinetic parameters by using statistical software Phoenix® WinNonlin® version 8.0 and SAS® System for Windows (Version: 9.2).

Analysis of variance (ANOVA) taking into account sequence, formulation, period and subject within sequence as fixed effects was performed on the ln transformed C_{max}, AUC_{0-t} and AUC_{0-inf} parameters (for ASA, Salicylic acid, Clopidogrel and Clopidogrel carboxylic acid) using the SAS® System GLM procedure. The period, sequence and treatment / formulation effects were tested at 5% level of significance.

Additionally, as the study was conducted in two groups, the Group*Formulation effect was added to the model. ANOVA model included group, sequence, subjects (group*sequence), period (group), formulation, group *formulation as the fixed effects on the ln transformed C_{max}, AUC_{0-t} and AUC_{0-inf} parameters (for ASA, salicylic acid, clopidogrel and clopidogrel carboxylic acid) using the SAS® System GLM procedure.

Bioequivalence between the Test (Treatment A) and Reference (Treatment B) was tested by the 90% confidence intervals for the ratio of the population geometric means (T/R) for the parameters.

Confidence intervals (CI) were determined for the ln- transformed AUC_{0-inf}, AUC_{0-t} and C_{max} for ASA, salicylic acid, clopidogrel and clopidogrel carboxylic acid using the treatments least squares means (LS-Means) and the residual values obtained from ANOVA.

Bioequivalence was concluded when the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptance range of 80.00 % -125.00% for ln-transformed C_{max} and AUC_{0-t} for aspirin and clopidogrel. Salicylic acid and clopidogrel carboxylic acid data was submitted as supportive evidence.

Results

The pharmacokinetic data were analysed as per the statistical method defined in the protocol. The data of 74 subjects were analysed using ANOVA model with the terms sequence, formulation, period and subject within sequence as the fixed effects. In addition, the significance of the group of formulation effect was tested.

Salicylic acid and clopidogrel carboxylic acid data was submitted as supportive evidence.

Clopidogrel

Table 8 Pharmacokinetic parameters for Clopidogrel (non-transformed values), N=74

Parameters (Units)	Un-transformed Data (Mean ± SD) n=74	
	Test Product (A)	Reference Product (B)
*T_{max} (hr)	0.833(0.333-2.750)	0.675(0.333-4.000)
C_{max} (pg/mL)	2758.776±3046.8817	2443.579±2551.0518
AUC_{0-t} (pg.hr/mL)	4201.323±4005.7516	3892.000±4053.3367
AUC_{0-inf} (pg.hr/mL)	4648.016±5133.4769	4030.268±4137.1327
K_{el} (1/hr)	0.176±0.0956	0.181±0.1291
$t_{½}$ (hr)	4.993±2.7612	5.150±2.4665
$(AUC_{0-t} / AUC_{0-inf}) * 100$	93.533±8.9307	94.948±4.3055

* Median, Minimum and Maximum values reported for T_{max}.

Table 9 Statistical analysis for Clopidogrel (ln-transformed values), N=74

Parameters (Units)	Geometric Least Squares Means				Ratio	Intra Subject CV (%)	90% Confidence Limits	Power (%)
	Test product (A)	n	Reference product (B)	n	(A / B) %		(A vs. B)	
C_{max} (pg/mL)	1617.408	74	1618.152	74	99.95	60.9	85.69-116.59	77.2
AUC_{0-t} (pg.hr/mL)	2782.432	74	2566.198	74	108.43	41.9	97.12-121.05	95.4
AUC_{0-inf} (pg.hr/mL)	2995.413	74	2705.646	74	110.71	43.6	98.76-124.11	94.2

Mean concentration-time profiles (semi-log and linear) of **Clopidogrel** are depicted in the two figures below.

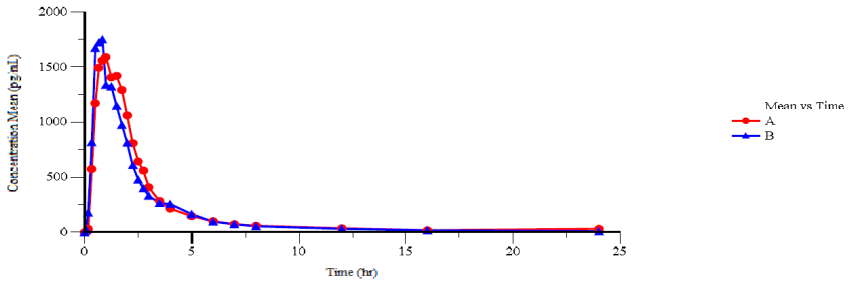

Figure 3 Linear Plot

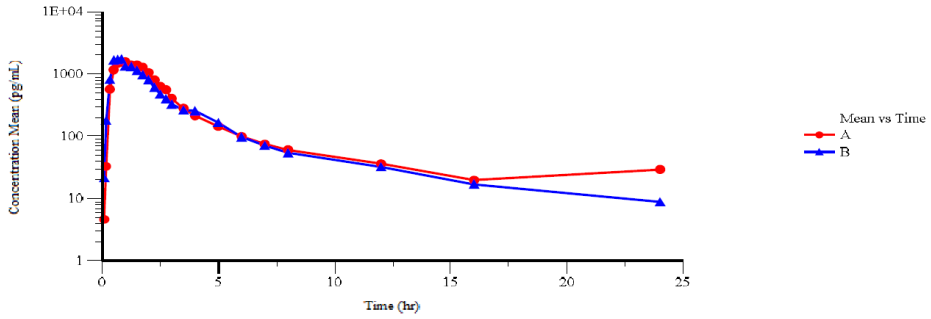

Figure 4 Semi Log Plot

Clopidogrel carboxylic acid

Table 10 Pharmacokinetic parameters for Clopidogrel carboxylic acid (non-transformed values); N=74

Parameters (Units)	Un-transformed Data (Mean ± SD) n=74	
	Test Product (A)	Reference Product (B)
*T_{max} (hr)	0.833(0.500-2.250)	0.666(0.500-4.000)
C_{max} (ng/mL)	4252.356±1543.8286	4583.116±1348.8626
AUC_{0-t} (ng.hr/mL)	10587.555±2411.7603	10692.896±2225.2810
AUC_{0-inf} (ng.hr/mL)	11694.600±2570.2335	11809.501±2673.0885
K_{el} (1/hr)	0.095±0.0281	0.098±0.0288
$t_{½}$ (hr)	7.918±2.4230	7.801±2.7394

Parameters (Units)	Un-transformed Data (Mean ± SD) n=74	
	Test Product (A)	Reference Product (B)
$(AUC_{0-t} / AUC_{0-inf}) * 100$	90.510±4.3273	90.971±4.4491

* Median, Minimum and Maximum values reported for T_{max}.

Table 11 Statistical analysis for Clopidogrel carboxylic acid (ln-transformed values); N=74

Parameters (Units)	Geometric Least Squares Means				Ratio	Intra Subject CV (%)	90% Confidence Limits	Power (%)
	Test product (A)	n	Reference product (B)	n	(A / B) %		(A vs. B)	
C_{max} (ng/mL)	3965.650	74	4383.289	74	90.47	27.6	83.99-97.45	99.9
AUC_{0-t} (ng.hr/mL)	10332.253	74	10470.221	74	98.68	8.3	96.46-100.95	100.0
AUC_{0-inf} (ng.hr/mL)	11429.858	74	11523.870	74	99.18	8.2	97.00-101.42	100.0

Mean concentration-time profiles (semi-log and linear) of **clopidogrel carboxylic acid** are depicted in the two figures below

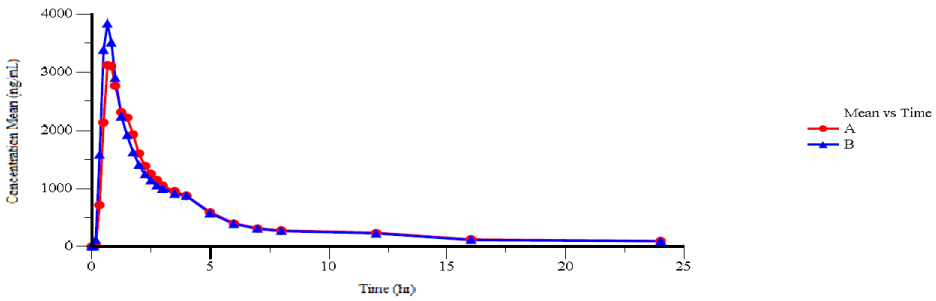

Figure 5 Linear Plot

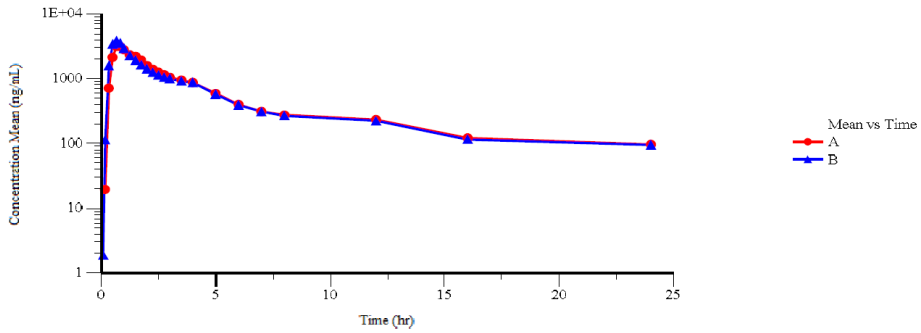

Figure 6 Semi Log Plot

Acetylsalicylic acid (ASA)

Table 12 Pharmacokinetic parameters for ASA (non-transformed values); N=74

Parameters (Units)	Un-transformed Data (Mean ± SD) n=74	
	Test Product (A)	Reference Product (B)
*T_{max} (hr)	0.500(0.166-1.500)	0.500(0.166-3.500)
C_{max} (ng/mL)	1704.602±634.3755	1501.737±527.6717
AUC_{0-t} (ng.hr/mL)	1328.178±249.9266	1278.215±229.6027
AUC_{0-inf} (ng.hr/mL)	1340.348±249.9293	1300.028±224.7168
K_{el} (1/hr)	1.874±0.3382	1.827±0.3802
$t_{½}$ (hr)	0.383±0.0765	0.412±0.2107
$(AUC_{0-t} / AUC_{0-inf}) * 100$	99.061±0.3182	98.521±4.4313

* Median, Minimum and Maximum values reported for T_{max}.

Table 13 Statistical analysis for ASA (ln-transformed values); N=74

Parameters (Units)	Geometric Least Squares Means				Ratio	Intra Subject CV (%)	90% Confidence Limits	Power (%)
	Test product (A)	n	Reference product (B)	n	(A / B) %		(A vs. B)	
C_{max} (ng/mL)	1584.427	74	1407.744	74	112.55	34.5	102.67-123.38	99.0
AUC_{0-t} (ng.hr/mL)	1305.580	74	1258.067	74	103.78	12.2	100.38-107.29	100.0
AUC_{0-inf} (ng.hr/mL)	1317.964	74	1278.095	74	103.12	11.5	99.92-106.42	100.0

Mean concentration-time profiles (semi-log and linear) of **ASA** are depicted in the two figures below.

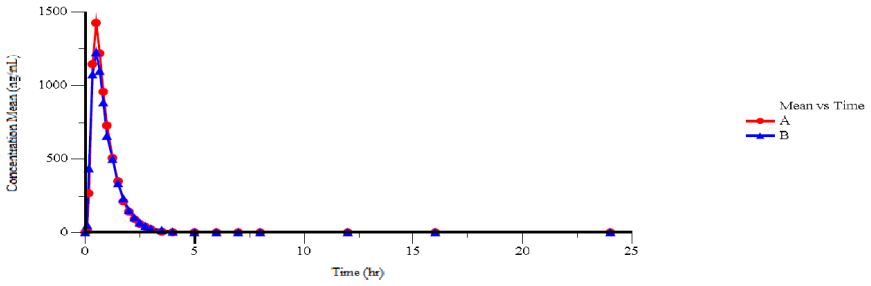

Figure 7 Linear Plot

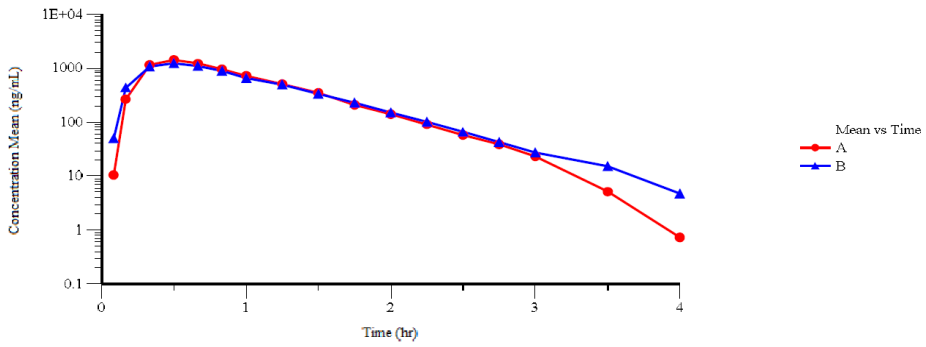

Figure 8 Semi Log Plot

Salicylic acid (SA)

Table 14 Pharmacokinetic parameters for SA (non-transformed values); N=74

Parameters (Units)	Un-transformed Data (Mean ± SD) n=74	
	Test Product (A)	Reference Product (B)
*T_{max} (hr)	1.000(0.500-3.000)	1.250(0.666-4.000)
C_{max} (ng/mL)	6677.158±1376.8771	6338.981±1314.7828
AUC_{0-t} (ng.hr/mL)	25887.119±11004.3183	25797.428±11736.1843
AUC_{0-inf} (ng.hr/mL)	26490.288±11880.999	26494.977±12714.0181
K_{el} (1/hr)	0.331±0.0796	0.328±0.0850
$t_{½}$ (hr)	2.277±0.8623	2.332±0.9972
$(AUC_{0-t} / AUC_{0-inf}) * 100$	97.961±1.4402	97.682±1.3840

* Median, Minimum and Maximum values reported for T_{max}.

Table 15 Statistical analysis for SA (ln-transformed values); N=74

Parameters (Units)	Geometric Least Squares Means				Ratio	Intra Subject CV (%)	90% Confidence Limits	Power (%)
	Test product (A)	n	Reference product (B)	n	(A / B) %		(A vs. B)	
C_{max} (ng/mL)	6537.997	74	6207.337	74	105.33	11.6	102.03-108.73	100.0
AUC_{0-t} (ng.hr/mL)	24433.548	74	24274.168	74	100.66	5.9	99.04-102.30	100.0
AUC_{0-inf} (ng.hr/mL)	24944.909	74	24852.733	74	100.37	5.6	98.85-101.92	100.0

Mean concentration-time profiles (semi-log and linear) of **SA** are depicted in the two figures below.

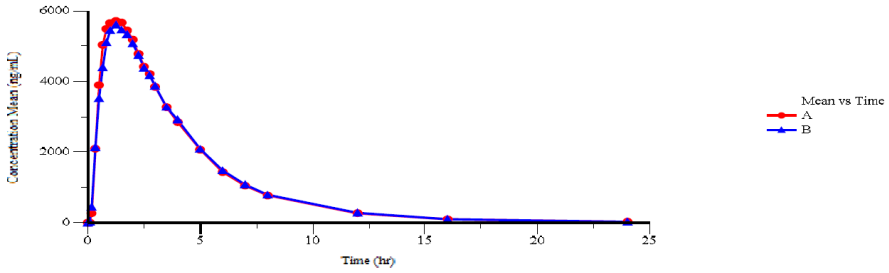

Figure 9 Linear Plot

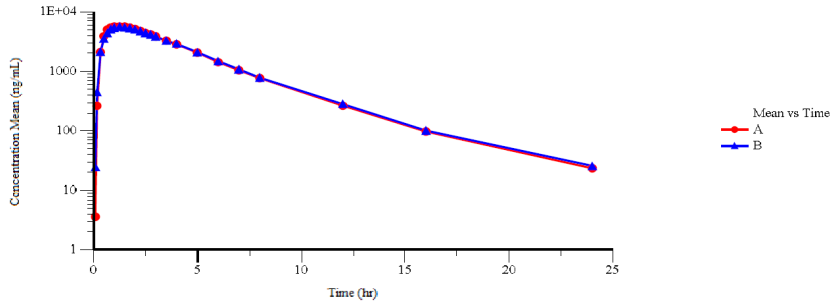

Figure 10 Semi Log Plot

Statistical p-value results from ANOVA model for primary parameters

Clopidogrel

Parameters	C_{max} (pg/mL)	AUC_{0-t}(pg.hr/mL)	AUC_{0-inf}(pg.hr/mL)
Formulation	0.9960	0.2249	0.1421
Sequence	0.8603	0.5897	0.5994
Period	0.0602	0.0455	0.0559

For AUC_{0-t} period effect was found statistically significant on ln-transformed scale with p-value 0.0455.

Clopidogrel carboxylic acid

Parameters	C_{max} (ng/mL)	AUC_{0-t}(ng.hr/mL)	AUC_{0-inf}(ng.hr/mL)
Formulation	0.0278	0.3349	0.5427
Sequence	0.7453	0.8587	0.8303
Period	0.2683	0.4043	0.4128

For C_{max} formulation/treatment effect was found statistically significant with respect to p-value 0.0278.

ASA

Parameters	C_{max} (ng/mL)	AUC_{0-t}(ng.hr/mL)	AUC_{0-inf}(ng.hr/mL)
Formulation	0.0354	0.0674	0.1102
Sequence	0.4953	0.5453	0.4365
Period	0.0944	0.5197	0.7467

For C_{max} formulation/treatment effect was found statistically significant with respect to p-value 0.0354.

SA

Parameters	C_{max} (ng/mL)	AUC_{0-t}(ng.hr/mL)	AUC_{0-inf}(ng.hr/mL)
Formulation	0.0082	0.5027	0.6877
Sequence	0.6017	0.2017	0.1959
Period	0.7269	0.6828	0.7940

For C_{max} formulation/treatment effect was found statistically significant with respect to p-value 0.0082.

Group Formulation Effect on Pharmacokinetic Parameters:

Clopidogrel

Parameters (Units)	Group*Formulation Effect P-value
	ln transformed
C_{max} (pg / mL)	0.6247
AUC_{0-t}(pg . hr / mL)	0.7054
AUC_{0-inf}(pg . hr / mL)	0.9123

Group*Formulation effect was found statistically insignificant for C_{max} AUC_{0-t} and AUC_{0-inf} on ln-transformed data for Clopidogrel.

Clopidogrel carboxylic acid

Parameters (Units)	Group*Formulation Effect P-value
	ln transformed
C_{max} (ng / mL)	0.4436
AUC_{0-t}(ng . hr / mL)	0.1260
AUC_{0-inf}(ng . hr / mL)	0.0707

Group*Formulation effect was found statistically insignificant for C_{max} AUC_{0-t} and AUC_{0-inf} on ln-transformed data for Clopidogrel carboxylic acid.

ASA

Parameters (Units)	Group*Formulation Effect P-value
	ln transformed
C_{max} (ng / mL)	0.8325
AUC_{0-t}(ng . hr / mL)	0.6338
AUC_{0-inf}(ng . hr / mL)	0.4096

Group*Formulation effect was found statistically insignificant for C_{max} AUC_{0-t} and AUC_{0-inf} on ln-transformed data for Aspirin.

Salicylic acid

Parameters (Units)	Group*Formulation Effect P-value
	ln transformed
C_{max} (ng / mL)	0.9279
AUC_{0-t}(ng . hr / mL)	0.3792
AUC_{0-inf}(ng . hr / mL)	0.4785

Group*Formulation effect was found statistically insignificant for C_{max} AUC_{0-t} and AUC_{0-inf} on ln-transformed data for Salicylic acid.

Justification provided by the applicant for significant formulation effect:

According to the Applicant, significant treatment effect or formulation effect can be present when the treatment mean square is small. Significant difference can occur at the moment the variability is low or the number of volunteers sufficiently high. Significant treatment effect or formulation effect can simply be ignored as the decision of equivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence boundaries.

Justification provided by the applicant for significant period effect:

According to the Applicant, significant period effect could possibly reflect different positioning, timing and degree of physical activity, timing and composition of food/beverages ingested, or the temperature of the water administered in the two periods. The conditions were maintained similar for both the periods; therefore it seems none of these are applicable in this study. However, it is possible that the psychological status of the subjects differed between the two periods, which may in turn effect on concentration data. The plasma samples of each subject of both the periods are analyzed all together and in a sequence in which the blood samples were collected. So there are very less chance of having analytical error. Also in each period both the products were dosed (Test and Reference), so period effect is not expected to influence the comparison of both the products using 90% confidence interval.

Missing sampling details

Time point (Hours)	Subject Number's
Period 1	
N/A	Nil
Period 2	
0.666 & 0.833	55
0.00-24.00	46
0.00-24.00	67

S.No.	Sample Details				
	Subject No.	Period No.	Time Points (Hrs)	Reason for Missing	No. of Samples
1	46	2	0.00 – 24.00	Withdrawn from the study due to his personal reasons	25
2	55	2	0.666 – 0.833	Difficulty to Access the vein for Recannulation	02
3	67	2	0.00 – 24.00	Withdrawn from the study due to non compliance to protocol	25
Total No. of Samples					52

Selection of PK parameters, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods chosen are considered appropriate.

No statistically significant group*formulation effect has been identified for C_{max}, AUC_{0-t} and AUC_{0-inf} on ln-transformed data for clopidogrel, ASA, clopidogrel carboxylic acid and salicylic acid.

A period effect with high statistical significance has been identified. With respect to the justification of the period effect provided by the Applicant, the psychological status of the subjects cannot be considered as a very likely reason for the effect observed. However, period effects have been observed for both the test and the reference product at the same time and are of limited relevance for the Bioequivalence conclusion.

No pre-dose levels of clopidogrel, clopidogrel carboxylic acid, ASA and SA are observed before period 2 drug administration indicating an adequate washout period.

No subject reached C_{max} at the first sample time, indicating that the sampling period is adequate.

Concentration time profiles (linear and semi-log) of clopidogrel, clopidogrel carboxylic acid, ASA and salicylic acid for each subject except for subject 46 and 67 are presented.

Based on the Clinical Study Report, subject 55 had two missing samples at 0.666 hours and 0.833 hours post-dose after treatment with the test product with no missing values affecting C_{max}/T_{max} for the reference product. Clarification about these two missing samples should be provided as no reference to it is made in the Protocol Deviations. Assessment of the importance of the data points from individual plasma concentration time curves suggests an imbalance in potentially relevant missing C_{max}/T_{max} points between test and reference. Thus, the pharmacokinetic profiles obtained for this subject are not adequately characterized for both Clopidogrel and acetylsalicylic acid. Therefore, the pharmacokinetic and statistical analysis should be redone removing this subject. The requested statistical analysis for the pivotal parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ with exclusion of subject no. 55 were provided by the Applicant during the evaluation. The results obtained demonstrated that the point estimate and 90%CI fall within the bioequivalence range 80-125%. Therefore, it can be concluded that bioequivalence between the test and reference medicinal products has been demonstrated with and without inclusion of that subject (no 55 initially included from this analysis).

Inconsistency in reporting have been found for AUC_{0-inf} untransformed data of ASA between one appendix and the clinical study report: measures of bioequivalence – untransformed AUC_{0-inf}; Geometric Least Square Means for Reference was reported as 1296.857 in the appendix while in the clinical study report it was reported 1300.028. The Applicant provided the requested clarification regarding differences in the reported value of ASA for AUC_{0-inf} reference product between the appendix and the clinical study report. The reported Arithmetic Least square means (untransformed) and arithmetic mean values for AUC_{0-inf} of ASA analyte were different for reference product due to unbalance reason as the elimination rate could not be estimated for subject no-14 in period-1. Any remaining doubts regarding inconsistency in reporting the data were thus resolved. The response provided by the applicant was considered acceptable.

Safety data

76 subjects were dosed in period-1 and 74 subjects in period-2 with a washout period of 9 days in group-I and 7 days washout period in group-II between the dosing days as per the randomization schedule.

Two subjects withdrew; one subject withdrew due to personal reasons and other subject was dismissed from the study before period 2 check-in due to positive test in UDS test.

There were no deaths and other serious adverse events and withdrawals due to (adverse events) AE over the course of the study. No new safety concerns related to administered formulations were reported during the conduct of this study. Adverse events observed in this study were in line with the known safety profile of the reference product.

Both the formulations were very well tolerated during the conduct of the study. Clinically significant changes were observed during post study safety assessment for five subjects, who received either test or reference products. The reported post study adverse events were mild in severity and possibly related to the study drug (Test or Reference). The case report forms for these 5 subjects were provided by the Applicant during the evaluation and upon review, no further concern was raised.

Conclusions

Based on the presented bioequivalence study, Clopidogrel/Acetylsalicylic acid Mylan 75/75 mg and 75/100 mg film-coated tablets is considered bioequivalent with DuoPlavin 75/75 mg and 75/100 mg film-coated tablets.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, the Applicant submitted a review of clinical data as well as one bioequivalence study.

The bioequivalence study was designed as a randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study to compare the bioavailability of 2 formulations of clopidogrel, clopidogrel carboxylic acid and ASA (75mg/100 mg) under fasting conditions.

The reference and test products are acceptable.

A signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation is provided.

76 healthy, adult, human subjects (Asian) were enrolled in accordance with protocol. The study was conducted in two groups and in each group, the subjects received one tablet of either test or reference product randomly as per the randomization schedule under fasting conditions. A 9 days washout separated each period in group-I and 7 days washout separated each period in group-II. 74 subjects completed the study were included in pharmacokinetic and statistical analysis. From Group II, 2 subjects withdrawn (subject number 46 & 67) prior dosing in period 2. The reason of the withdrawal is acceptable. Case Report Form for subjects No.: 46 and 67 were provided in Day 180 response to the Rapporteur's request.

With regard to validation of the bioanalytical method, the Applicant provided some clarifications during the evaluation which were considered satisfactory. During the evaluation, the Applicant was requested to demonstrate the lack of occurrence of a potential back-conversion of clopidogrel carboxylic acid metabolite to the parent-drug (unchanged clopidogrel). The experimental data obtained and presented by the Applicant during the evaluation demonstrated that samples of clopidogrel spiked with therapeutically relevant concentrations of the clopidogrel carboxylic acid do not undergo back-conversion to the metabolite to the parent compound. This was demonstrated for all conditions that occurred throughout the sample collection, processing, analysis and storage. Thus, there is no impact on the reported concentrations for the study and the reported concentrations are valid, reliable and reproducible.

A discrepancy noted between the Applicant's Bioanalytical study report C18156_CLO and selectivity experiment was resolved. Missing certificate of analysis for all the reference standards were provided by the Applicant during the evaluation.

The statistical software and method used for the pharmacokinetic analyses are considered acceptable. The ANOVA model used is adequate for a bioequivalence study.

The pharmacokinetics parameters measured/calculated are standard for a single-dose study. They are acceptable and according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Based on the Clinical Study Report, subject 55 had two missing samples at 0.666 hours and 0.833 hours post-dose after treatment with the test product with no missing values affecting Cmax/Tmax for the reference product. Clarification about these two missing samples should be provided as no reference to it is made in the Protocol Deviations. Assessment of the importance of the data points from individual plasma concentration time curves suggests an imbalance in potentially relevant missing Cmax/Tmax points between test and reference. Thus, the pharmacokinetic profiles obtained for this subject are not adequately characterized for both Clopidogrel and acetylsalicylic acid. Therefore, the pharmacokinetic and statistical analysis should be redone removing this subject. The requested statistical analysis for the pivotal parameters Cmax AUC_{0-t} and $AUC_{0-\infty}$ with exclusion of subject no. 55 were provided by the Applicant during the evaluation. The results obtained demonstrated that the point estimate and 90%CI fall within the bioequivalence range 80-125%. Therefore, it can be concluded that bioequivalence between the test and reference medicinal products has been demonstrated with and without inclusion of that subject (no 55 initially included from this analysis).

Inconsistency in reporting have been found for AUC0-inf untransformed data of ASA between one appendix and the clinical study report: measures of bioequivalence – untransformed AUC_{0-inf}; Geometric Least Square Means for Reference was reported as 1296.857 in the appendix while in the clinical study report it was reported 1300.028. The Applicant provided the requested clarification regarding differences in the reported value of ASA for AUC_{0-inf} reference product between the appendix and the clinical study report. The reported Arithmetic Least square means (untransformed) and arithmetic mean values for AUC_{0-inf} of ASA analyte were different for reference product due to unbalance reason as the elimination rate could not be estimated for subject no-14 in period-1. Any remaining doubts regarding inconsistency in reporting the data were thus resolved. The response provided by the applicant was considered acceptable.

With regard to the safety data, adverse events observed in this study were in line with the known safety profile of the reference product. The two formulations were very well tolerated during the conduct of the study.

The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00% for both clopidogrel and acetylsalicylic acid. Bioequivalence of the two formulations was demonstrated.

The Applicant applied for a biowaiver for the 75 m/75 mg strength. The *in vivo* bioequivalence study for the lowest strength of 75mg/75 mg can be waived as long as all biowaiver criteria are fulfilled. The (a)- (c) criteria defined in the BE guideline are fullfilled as the pharmaceutical products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths are quantitatively proportional.

In the case of the criterion (d) of the BE Guideline, the Applicant has provided comparative dissolution data. The dissolution profile data was generated for test batches of clopidogrel and acetylsalicylic acid tablets 75 mg/75 mg and 75 mg/100 mg in different pH conditions like 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and release media. The similarity factor (f2 value) were calculated between bio-batch and lower strength batch. The bootstrap calculation method is used for calculation of similarity factor as higher RSD was observed in one buffer for one of the drug substance. Both batches express similar dissolution profile for both Clopidogrel and Acetylsalicylic acid across the pH range of 1.2 to 6.8.

However, concerning the dissolution methodology, the selected rotation speed instead of 50rpm which seems to result in a rapid drug release, typically leading to a reduced discriminating power of the dissolution test. According to the BE Guideline the usual rotation speed used with paddle-apparatus II is 50 rpm.

The Applicant satisfactorily justified the selection of agitation speed for this product instead of 50 rpm. New comparative dissolution study results between the lower strength (75/75 mg) and bio-strength (75/100mg) of the test product at rotation speed of 50 rpm in QC release media were provided. The dissolution study results generated at agitation speed of 50 rpm showed incomplete drug release after 45 min and higher % RSD in the earlier time points for both clopidogrel and acetylsalicylic acid. Whereas less variability and complete release was observed for clopidogrel and acetylsalicylic acid at selected agitation speed. However, calculation of f2-values in the case above is not allowed as the RSD values at the early time points were too high. The Applicant has performed the bootstrapping for calculation of similarity factor for the dissolution profiles at agitation speed of 50 rpm where the RSD value is found to be higher at the early time points. The summary of bootstrap analysis and similarity factor calculation for dissolution profiles at agitation speed of 50 rpm in different mediums showed that f2 was more than 50 but lower limit (5th percentile) of the 90% CI of f2 was observed to be slightly less than 50 for some of the dissolution profiles of Clopidogrel and Acetylsalicylic acid.

Furthermore, the Applicant provided the requested photographs for visual observation of dissolution of Clopidogrel and Acetylsalicylic acid tablets 75/75mg and 75/100 mg at both 50 & selected rpm. The presented photographs show unstirred contents (coning) at bottom of dissolution vessel at 50 rpm whereas less unstirred contents is observed at selected rpm after 20 min, 30 min and 45 min. Thus, the selection of agitation speed of 75 rpm for in vitro dissolution tests is considered appropriate.

However, after reviewing dissolution profiles comparisons for clopidogrel, it was noted that the 90% confidence interval of the f2 obtained from the bootstrap method was not reported in the presented documentations. The Applicant provided the requested similarity factor calculation including 90% confidence interval for bootstrap statistical evaluation of dissolution profiles for one of the drug component.

In order to justify the exclusion of the first sampling time point, the Applicant provided during the evaluation results of disintegration time observed at compression stage (un-coated) of clopidogrel and acetylsalicylic acid tablets. The above data indicated that core tablets of both strengths are having a longer disintegration time. Taking into consideration that clopidogrel and acetylsalicylic acid tablet is a bilayer tablet which consists of two separate layers of clopidogrel and acetylsalicylic acid and having a longer disintegration time and the higher variability in dissolving of film coating layers in earlier time points of dissolution profile study will not have any impact on in-vivo performance of clopidogrel and acetylsalicylic acid, the exclusion of the first sampling point is considered justified.

Furthermore, the Applicant performed during the evaluation the dissolution profile study for two other pilot scale batches of clopidogrel and acetylsalicylic acid tablets 75/75 mg and clopidogrel and acetylsalicylic acid tablets 75/100 mg. Comparison of dissolution profiles shows that the above batches of both strengths express similar dissolution profiles to that of bio batch (BEQ) for both active substances. However, the Applicant performed dissolution testing with the selected agitation speed which is not adequately justified.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The Applicant committed to perform comparative dissolution profile on the production scale batches of Clopidogrel and Acetylsalicylic Acid 75mg/75mg and 75mg/100mg film-coated tablets. The results will be provided at a Competent Authority's request or if the dissolution profiles are not similar together with proposed action.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study, Clopidogrel/Acetylsalicylic Acid Mylan 75/75 mg and 75/100 mg film-coated tablets can be considered bioequivalent with the reference product DuoPlavin 75/75 mg and 75/100 mg film-coated tablets. Approval of Clopidogrel/Acetylsalicylic Acid Mylan can be supported from a clinical point of view.

2.5. Risk management plan

The applicant identified the following safety concerns in the RMP, version 1.2:

Safety concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	none

Pharmacovigilance plan

No additional pharmacovigilance activities are planned. Routine pharmacovigilance activities are sufficient to minimise the risks of the product.

Risk minimisation measures

No additional risk minimisation measures are planned. Routine risk minimisation measures are sufficient to manage the safety concerns of the medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. 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

This application concerns a generic version of clopidogrel/acetylsalicylic acid film-coated tablets. The reference product DuoPlavin is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoPlavin is a 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

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substances clopidogrel and acetylsalicylic acid was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover design to compare the bioavailability of 2 formulations of clopidogrel, clopidogrel carboxylic acid and ASA (75mg/100 mg) under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements.

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Clopidogrel/Acetylsalicylic acid 75/100 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the DuoPlavin 75/100 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00% for both clopidogrel and acetylsalicylic acid. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Clopidogrel/Acetylsalicylic acid Mylan is favourable in the following indication:

Clopidogrel/Acetylsalicylic acid Mylan is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Clopidogrel/Acetylsalicylic acid Mylan is a 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 CHMP 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.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

Appendix

N/A