16 December 2021
EMA/27581/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sitagliptin/Metformin hydrochloride Mylan

International non-proprietary name: metformin hydrochloride / sitagliptin hydrochloride monohydrate

Procedure No. EMEA/H/C/005678/0000

Note

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

Administrative information

Name of the medicinal product:	Sitagliptin/Metformin hydrochloride Mylan
Applicant:	Mylan Ireland Limited Unit 35/36 Grange Parade Baldoyle Industrial Estate Dublin 13 IRELAND
Active substance:	metformin hydrochloride / sitagliptin hydrochloride monohydrate
International Nonproprietary Name/Common Name:	metformin hydrochloride / sitagliptin hydrochloride monohydrate
Pharmaco-therapeutic group (ATC Code):	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS, Combinations of oral blood glucose lowering drugs (A10BD07)
Therapeutic indication(s):	For adult patients with type 2 diabetes mellitus: Sitagliptin/Metformin hydrochloride Mylan is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. Sitagliptin/Metformin hydrochloride Mylan is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. Sitagliptin/Metformin hydrochloride Mylan is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a

	thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. Sitagliptin/Metformin hydrochloride Mylan is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	50 mg / 850 mg and 50 mg / 1000 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PE/PVdC/Alu) and bottle (HDPE)
Package size(s):	14 tablets, 14 x 1 tablets (unit dose), 196 tablets, 56 tablets, 56 x 1 tablets (unit dose), 60 x 1 tablets (unit dose) and 90 tablets

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List of abbreviations

AE - adverse event

ASMF - Active substance master file

AUC - Area Under the plasma Concentration

AUC0-inf - Area Under the plasma Concentration-time curve from time zero to infinity

AUC0-t - Area Under the plasma Concentration-time curve from time zero to t hours

BA - bioavailability

BE – Bioequivalence

BMI - Body Mass Index

CEP - Certificate of Suitability of the European Pharmacopoeia

CHMP - Committee for Medicinal Products for Human use

CI - confidence interval

Cmax - maximum plasma concentration

CQA - Critical quality attribute

CRO - Certified Research Organisation

CYP – cytochrome

DPP-4 inhibitor - inhibitor of the dipeptidyl peptidase 4

EC - European Commission

ECG – Electrocardiogram

EDQM - European Directorate for the Quality of Medicines

EMA - European Medicines Agency

EU - European Union

FPG - fasting plasma glucose

GCP - Good Clinical Practice

GC - Gas chromatography

GC-MS/MS - Gas chromatography mass spectrometry/mass spectrometry

GI - gastrointestinal

GIP - glucose-dependent insulinotropic polypeptide

GLP-1 - glucagon-like peptide-1

HbA1c - glycated haemoglobin

HDPE - High density polyethylene

HPLC - High performance liquid chromatography
HRMS - High resolution mass spectrometry

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS - Inductively coupled plasma mass spectrometry

IEC - Independent Ethics Committee

IR – Infrared

KF - Karl Fischer titration

MA - Marketing Authorisation

MAH - Marketing Authorisation holder

MHRA - British National Competent Authority

NDMA - *N*-Nitrosodimethylamine

NMR - Nuclear Mmagnetic resonance

NMT - Not more than

PD - Pharmacodynamics

PDE - Permitted daily exposure

PE - Polyethylene

Ph. Eur. - European Pharmacopoeia

PPG - prandial plasma glucose

PVC - Polyvinyl chloride

PVDC - Polyvinylidene chloride

QC - Quality control

QOS - Quality Overall Summary

QTPP - Quality target product profile

RH - Relative Humidity

SmPC - Summary of product characteristics

tmax - time to achieve maximum plasma concentration

TLC - Thin layer chromatography

T2DM - Type 2 diabetes mellitus

$t_{1/2}$ - elimination half-life time

UV – Ultraviolet

Vd - volume of distribution

XRPD - X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 4 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Sitagliptin/Metformin hydrochloride Mylan, 50 mg / 850 mg and 50 mg / 1000 mg, 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 25 June 2020.

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 the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> For adult patients with type 2 diabetes mellitus:
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
>
> Sitagliptin/Metformin hydrochloride Mylan is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

1.2. Legal basis, dossier content

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, a bioequivalence study with the reference medicinal product Janumet and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg

- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 16-07-2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/455

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

- Product name, strength, pharmaceutical form: Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 16-07-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/455

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:

- Product name, strength, pharmaceutical form: Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 16-07-2008
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/08/455
- Bioavailability study number(s): SIME-1-19123, SIME-1-19124, C18136, C18137

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Elita Poplavska

The application was received by the EMA on	4 November 2020
The procedure started on	26 November 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	02 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 March 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	06 August 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 October 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	15 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
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 Sitagliptin/Metformin hydrochloride Mylan on	16 December 2021

2. Scientific discussion

2.1. Introduction

The application for marketing authorisation of Sitagliptin/Metformin hydrochloride Mylan 50 mg/850 mg and 50 mg/1000 mg film-coated tablets is submitted under Article 10(1) of Directive 2001/83/EC, as amended (i.e. a generic MA application). The reference product is Janumet, film-coated tablet, 50 mg/850 mg and 50

mg/1000 mg marketed by Merck Sharp and Dohme B.V., that was first approved in the European Union on 16 July 2008 via the centralised procedure (EU/1/08/455).

The active substances of Sitagliptin/Metformin hydrochloride Mylan are sitagliptin and metformin hydrochloride, two oral blood glucose-lowering drugs used in combination in the treatment of type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by elevated levels of blood glucose, which prevalence has been increasing steadily all over the world. Type 2 diabetes mellitus is due primarily to lifestyle factors and genetics. Type 2 diabetes mellitus is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. In type 2 diabetes mellitus, the body does not produce enough insulin or the cells ignore the insulin. Over time, high blood sugar levels can increase the risk for serious complications, including serious damage to the heart, blood vessels, eyes, kidneys and nerves.

Sitagliptin is an active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4 inhibitor) that has been approved for the therapy of type 2 diabetes. Sitagliptin 100 mg daily was well tolerated and provided effective and sustained improvement in HbA1c, FPG and PPG levels. Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin metabolizes the naturally occurring incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.

Metformin is the most commonly prescribed therapy for patients with T2DM. It has a good safety profile and is associated with low cost. Metformin is high efficiency in reducing fasting and postprandial blood glucose and lowering glycosylated hemoglobin in patients. The hypoglycemic effect of metformin is closely related to its capabilities in suppression of hepatic glucose production and intestinal glucose absorption, and promotion of β-cell functions and insulin sensitivity. Metformin increases insulin release and cell viability at the presence of glucose or free fatty acids. In addition, it also decreases lipogenesis in the liver, muscles, and fat, inhibits lipolysis in fat and increases glucose utilization and GLP-1 secretion.

The indications applied for Sitagliptin/Metformin hydrochloride Mylan are the same as those for the reference product Janumet:

> For adult patients with type 2 diabetes mellitus:
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
>
> Sitagliptin/Metformin hydrochloride Mylan is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing sitagliptin hydrochloride monohydrate and metformin hydrochloride as active substances in a fixed dose combination. Two strengths are applied for: 50 mg/850 mg film coated tablets and 50 mg/1000 mg film-coated tablets.

Each 50 mg/850 mg film-coated tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin free base and 850 mg of metformin hydrochloride.

Each 50 mg/1000 mg film-coated tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin free base and 1000 mg of metformin hydrochloride.

Other ingredients are:

Tablet core: microcrystalline cellulose, anhydrous colloidal silica, croscarmellose sodium, sodium lauryl sulphate, povidone and sodium stearyl fumarate;

Film-coating: polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172) (50/850 only) and black iron oxide (E172) (50/1000 only).

The product is available in PVC/PE/PVDC/Alu blisters and HDPE bottles with white opaque polypropylene screw cap with aluminium induction sealing liner wad as described in section 6.5 of the SmPC.

2.2.2. Active substance – Sitagliptin Monohydrate

General information

The documentation on the active substance is presented using an active substance master file (ASMF) procedure.

The chemical name of sitagliptin hydrochloride monohydrate is 7-((3*R*)-3-amino-1-oxo-4-(2, 4, 5-trifluorophenyl) butyl]-5, 6, 7, 8-tetrahydro-3-(trifluoro methyl)-1, 2, 4-triazolo (4, 3-a] pyrazine hydrochloride monohydrate corresponding to the molecular formula $C_{16}H_{15}F_6N_5O.HCl.H_2O$ It has a molecular mass of 461.79 g/mol (salt/hydrate form) or 407.32 (free base) and the following structure:

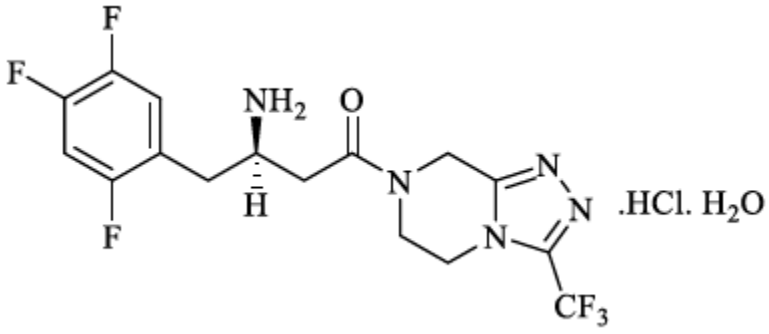

Figure 1: active substance structure

The chemical structure of sitagliptin hydrochloride monohydrate was confirmed by a combination of UV spectroscopy, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The presence of the hydrated form was confirmed by thermogravimetric analysis. X-ray powder diffraction (XRPD) was used to characterise the crystalline form.

Sitagliptin hydrochloride monohydrate is a white to off-white slightly hygroscopic crystalline powder, freely soluble in aqueous media across the physiological pH range. It contains a single chiral centre which is introduced selectively in the synthetic process. Enantiopurity is determined by a chiral HPLC method in the active substance specification.

Polymorphism was investigated extensively, and many different hydrated and solvated forms were identified. The commercial crystallisation conditions for isolation of the active substance ensure that the monohydrate is formed routinely. It was also demonstrated in stability studies that this form is stable during storage.

Manufacture, characterisation and process controls

Sitagliptin hydrochloride monohydrate is synthesized convergently in 6 main stages using two well defined starting materials with acceptable specifications.

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 crystallisation conditions in the last stage ensure the correct solvate and polymorphic form is produced routinely.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The assessment and control of potentially mutagenic impurities was not adequately documented in the initial submission. In addition, the risk of mutagenic impurities from the starting materials had not been explained, resulting in a major objection. In response, the applicant provided a clear explanation of the hazard assessments conducted, as well as the risk assessment of the starting materials. The control strategy was further justified. The revised risk assessment and control strategy for mutagenic impurities is in line with ICH M7.

The active substance is packaged in a single polyethylene (PE) bag, twisted and tied with a plastic fastener. The PE bag is inserted in a triple laminated aluminium bag and sealed. These bags are further packed in HDPE drums. The primary contact material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification shown in Table 1 includes tests for appearance, solubility (Ph. Eur.), identity (IR, HPLC), identity of chloride (Ph. Eur.), polymorphic form (XRPD), water content (KF), sulphated ash (Ph. Eur.), hydrochloride content (potentiometry), enantiomer content (chiral HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), and particle size distribution (laser diffraction).

Limits for impurities have been set in line with ICH Q3A. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. No test for microbiological quality is needed as batch data demonstrates that levels are routinely below pharmacopoeial limits for non-sterile active substances. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, identification by XRPD, water content, content of (*S*)-isomer, related substances, assay. The analytical methods used were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed and all remained within specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance is photostable.

The active substance was also exposed to stressed conditions. In aqueous acid or base, degradation occurs. However, sitagliptin is stable to heat and oxidation. In the solid state, the active substance is stable with respect to heat and humidity.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container at or below 25°C.

2.2.3. Active substance – Metformin Hydrochloride

General information

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride corresponding to the molecular formula $C_4H_{11}N_5.HCl$. It has a molecular mass of 169.6 g/mol and the following structure:

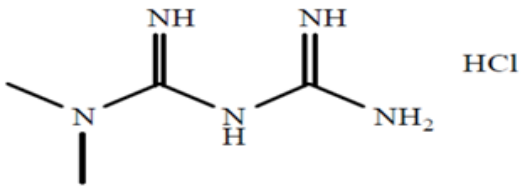

Figure 2: active substance structure

Metformin hydrochloride is a white or almost white crystalline solid, freely soluble in aqueous media across the physiological pH range. Polymorphic form is confirmed by XRPD in the active substance specification.

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

Manufacture, characterisation and process controls

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

Specification

The active substance specification shown in Table 2 includes pharmacopoeial tests for appearance, solubility (Ph. Eur.), identity (melting point, IR, TLC, colour development, reaction of chlorides, all Ph. Eur.), appearance of solution (Ph. Eur.), impurities (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.) and assay (HPLC). Additional tests are carried out by the finished product manufacturer for residual solvents (GC), particle size (laser diffraction), polymorphic form (XRPD) and microbial enumeration (Ph. Eur.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Limits for particle size were set in line with batches used to manufacture finished product for the bioequivalence studies.

The non-compendial analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 2 production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

The re-test period and packaging material are stated on CEP and are as follows: 5 years if stored in double polyethylene bags, placed in either cardboard box or fiber drum or polyethylene drum.

2.2.4. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets containing sitagliptin hydrochloride monohydrate and metformin hydrochloride as active substances in a fixed dose combination. Two strengths are proposed to be authorised:

- 50 mg/850 mg film-coated tablets are pink, capsule shaped, biconvex, bevelled edge tablet, debossed with 'M' on one side of the tablet and 'SM5' on the other side.
- 50 mg/1,000 mg film-coated tablets are peach to brown, capsule shaped, biconvex, bevelled edge tablet, debossed with 'M' on one side of the tablet and 'SM7' on the other side.

The two strengths can be sufficiently differentiated by colour and debossing.

The aim of the pharmaceutical development was to develop a generic product that is essentially similar and bioequivalent to the reference product, Janumet. The generic product was developed containing the same two strengths as the reference product. Metformin hydrochloride is used in both products. However, in the generic product, sitagliptin hydrochloride monohydrate is used instead of sitagliptin phosphate monohydrate used in the reference product which is acceptable according to Directive 2001/83/EC. Different salts of an

active substance are considered to be the same active substance, if they not differ significantly in properties with regard to safety and efficacy (see section 2.4.1 for clinical justification). The majority of the excipients are the same in both products. However, the generic product additionally includes croscarmellose sodium and colloidal silica in the core tablet and iron oxide yellow is used in the film-coating of 50 mg/850 mg strength instead of iron oxide black. Compatibility of each excipient with both active substances was demonstrated. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Physicochemical properties of both active substances have been sufficiently discussed in the dossier with respect to particle size distribution, bulk and tapped density, compressibility index and Hausner ratio and solubility. Both active substances are freely soluble in aqueous media across the physiological pH range and both exhibit polymorphism. Stability of polymorphic form during manufacturing and storage of finished product was demonstrated for both active substances.

A quality target product profile (QTPP) was established for the generic product focussing on essential similarity with the reference product and pharmacopoeial requirements. Based on risk assessments, the attributes of the finished product most likely to be impacted by formulation development were identified as content uniformity, impurities and dissolution. These were defined as the critical quality attributes (CQAs).

Both active substances exhibit poor flow properties. Several prototype formulations were developed to investigate the impact of different excipient contents and process parameters on the identified CQAs. Metformin hydrochloride is the main constituent of the tablets. The selection of the manufacturing process is described adequately. The process parameters of the intermediate stages were optimised to ensure the CQAs are achieved. The developed process has been shown to be suitable to handle the active substance properties and produce tablets of acceptable content uniformity. Impurity content of the generic and reference products were shown to be sufficiently similar.

Bioequivalence was demonstrated in clinical studies under both fed and fasted conditions. In addition, comparative *in vitro* dissolution studies in 3 dissolution media (pH 1.2, 4.5 and 6.8) were performed between test and reference products. Less than 85% of the active substances had been released after 15 minutes and so f2 values were calculated to demonstrate similarity of dissolution profiles in line with the requirements of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98). The f2 values were found to be greater than 50 in all the media studied. Therefore dissolution profiles can be considered similar.

Since both active substances are freely soluble, the dissolution method was developed considering the expected *in vivo* release characteristics. A suitable medium with the paddle appararus was selected, and the volume and paddle speed were justified. Discriminatory power was investigated with respect to meaningful changes in relevant process parameters. In each case, a 20-25% change in dissolution time was observed. Given the inherent high solubility of the active substances, the QC dissolution method and discriminatory power were considered adequate once the release specification has been tightened at the request of CHMP.

The primary packaging is PVC/PE/PVDC-Alu blisters or HDPE bottles with white opaque polypropylene screw caps with aluminium induction sealing liner wads. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process involves wet granulation of metformin with intra-granular excipients followed by drying and milling; blending with sitagliptin and extra-granular excipients; compression; tabletting; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated for 3 batches of each strength at the minimum scale defined in the dossier. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical steps of the process were identified and justified. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. An acceptable validation scheme has been included in module 3.2.R which documents steps that will be taken to validate the process on the maximum scale defined in the dossier.

Product specification

The finished product release specifications for the 50/850 mg tablets shown in Table 6 include appropriate tests for this kind of dosage form including description, dimensions, identification (HPLC, UV), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), water content (KF), microbiological quality (Ph. Eur.), presence of TiO_2 and iron oxide (colour tests) and *N*-nitrosodimethylamine (NDMA, GC-MS/MS). The specifications for the 50/1000 mg tablet are the same except for the description, dimension, and absolute mass listed in the assay calculation.

Related substances are limited in line with ICH Q3B. Limits for total impurities, dissolution and water content were tightened at the request of CHMP. The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data from multiple batches of each strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The finished product contains metformin which contains dimethyamine as an impurity and is known to be susceptible to formation of NDMA during formulation. The applicant initially claimed that there was no risk of NDMA formation and provided data from multiple batches of finished product where NDMA was not detected. However, the analytical method was not considered sensitive enough and there was no discussion of an actual control strategy for prevention of NDMA formation. In line with what is currently requested of all MAHs for metformin-containing products, a major objection was raised asking for routine control of NDMA. In response, the applicant introduced a routine test for NDMA in the finished product specification and explained that the blister packaging used will not contain nitrocellulose.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 batches of finished product each strength stored for up to 18 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in both of the primary packaging proposed for marketing. For the HDPE bottles, a bracketing approach was taken given that the bottles contain 30, 90 or 196 tablets. Only the extreme counts were tested which was considered justified in line with ICH Q1D. Samples were tested for description, assay, dissolution, related substances, water content and microbiological quality. The analytical procedures used are the same as for release testing and are stability indicating. No significant trends were observed for any of the measured parameters which all remained within specification. For the later timepoints, dissolution results met with the limit that was tightened during the procedure. In addition, NDMA was not detected at the later timepoints.

In addition, 1 batch of each strength stored in each packaging format (including the extremes of the bottle count) were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product was found to be photostable irrespective of packaging format or strength.

An open pot study for up to 90 days was conducted in lieu of an in-use study. All tested parameters remained within specification. However, it was not possible to test for NDMA since all samples had been discarded before the specification limit was added. Therefore, the CHMP asked the applicant to start a new open pot study and the applicant committed to informing the agency should any out of specification results be obtained (REC). However, given the provided data from long term and accelerated studies, it is not expected that NDMA will be formed to any appreciable amount.

A bulk stability study was conducted on 3 batches of each strength, stored for up to 6 months under long term and accelerated conditions. No significant changes were observed to any of the measured parameters and a bulk holding time of 12 months without temperature restriction is justified.

Based on available stability data, the proposed shelf-life of 2 years without specific storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, the applicant provided a revised risk assessment and hazard assessment for potential mutagenic impurities in sitagliptin in order to address a major objection.

The second major objection relating to the potential presence of NDMA in the finished product was resolved by addition of a specification limit in line with the acceptable intake. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to measuring NDMA content in the finished product at the end of a second open pot study. This point is put forward and agreed as recommendations for future quality development.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation for future quality development

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 is recommended to conduct a further open pot study on the finished product and measure the NDMA content at the end of the study and inform the agency should any out of specification results be obtained.

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. Pharmacology

Sitagliptin and metformin hydrochloride are two different types of antihyperglycaemic agents with complementary mechanisms of actions for lowering blood glucose.

Sitagliptin is a competitive inhibitor of dipeptidyl peptidase (DPP-4), an enzyme that degrades incretin peptides glucagon-like-peptide-1 (GLP-1) and glucose-dependent-insulinotropic peptide (GIP). Pharmacologically, sitagliptin has a very high selectivity for DPP-4 with concentrations of 50% inhibition (IC50) in the range of 13-69 Nm in rodents, dogs and humans, but with a minimal inhibition against closely related proteases including DPP-8/9 and a panel of unrelated enzymes and ion channels.

Metformin is a biguanide that has been used for glycaemic control in T2DM patients since 1959 in the European market. Current literature suggest that metformin exerts its BG lowering effect through complicated mechanisms which involve reduction in hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis, improvement of insulin sensitivity via potentiation of peripheral glucose uptake and utilization and inhibition of intestinal glucose absorption.

2.3.3. Pharmacokinetics

The pharmacokinetics of sitagliptin and metformin hydrochloride is well known. New non-clinical pharmacokinetic studies have not been conducted and it is considered acceptable for generic application. Pharmacokinetic studies conducted with sitagliptin/metformin fixed-dose combination products were not identified in the literature, however, there were no pharmacokinetics drug-drug interaction between the two components. Therefore, the pharmacokinetics studies for sitagliptin and metformin hydrochloride have been separated.

2.3.4. Toxicology

Published toxicity data, including single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity were provided. No new specific data submitted.

Non-clinical aspects of the Section 4.6 and 5.3 of the proposed SmPC are in line with the reference product and published scientific literature and considered acceptable.

No preclinical studies have been conducted with the sitagliptin/metformin hydrochloride fixed-dose combination to evaluate the acute toxicity, genotoxicity, carcinogenicity and reproductive and development toxicity. The bridging toxicological data demonstrating a lack of exacerbated toxicity when sitagliptin was co-administrated with metformin hydrochloride in dogs (the most sensitive toxicological species) are considered sufficient to support the safety of the sitagliptin/metformin hydrochloride fixed-dose combination products.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment including PECsurfacewater calculation and information about logKow is submitted. The PEC values for both metformin hydrochloride and sitagliptin are above the action limit of 0.01 µg/L, therefore, Phase II studies are necessary. The PNECsurfacewater for metformin has calculated by applying an assessment factor of 10 to the lowest NOEC from multiple chronic studies with algae, daphnids and fish. The PNECsurfacewater for sitagliptin has calculated by applying an assessment factor of 10 to the lowest NOEC from a study with *Pseudokirchneriella subcapitata* (green algae). The PECsurfacewater to PNECsurfacewater ratio (risk quotient) for both metformin hydrochloride and sitagliptin is below 1, and it can be concluded that the active substances are unlikely to represented risk for aquatic environment.

The logKow values for both metformin hydrochloride and sitagliptin are below the action limit 4.5, no further PBT (Persistence, Bioaccumulation, Toxicity) assessment is deemed necessary.

2.3.6. Discussion on non-clinical aspects

The range of non-clinical data presented in the dossier is appropriate for a generic application. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. ERA is considered acceptable.

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

2.3.7. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Sitagliptin/Metformin hydrochloride Mylan was provided and was accepted by the CHMP. Additional non-clinical studies were not considered necessary. The product is considered approvable from a non-clinical viewpoint.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing sitagliptin and metformin hydrochloride. To support the application, the Applicant has submitted four bioequivalence studies. Bioequivalence studies have been performed with both strengths and under both fasted and fed conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version is of particular relevance.

Human pharmacology, efficacy and safety of metformin and sitagliptin are well known. The updated clinical overview on human pharmacology, efficacy and safety of metformin and sitagliptin is considered appropriate.

In the clinical overview the Applicant has provided a justification for the use of an alternative salt (hydrochloride monohydrate) for sitagliptin, as a phosphate salt is used for sitagliptin in the reference product. The Applicant states that there are no pharmacological or toxicological objections against the use of this salt in the proposed indications compared to the phosphate salt and that the different salt of the active substance sitagliptin does not differ significantly in properties with regards to safety and efficacy. The hydrochloride salt also does not differ significantly in physico-chemical properties from the phosphate salt and both salts are highly soluble. The provided justification is considered acceptable.

The clinical aspects of the Summary of Product Characteristics (SmPC) are in line with the SmPC of the reference products with amendments presented in the annexed product information.

GCP aspect

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.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

To support the application, the Applicant has submitted four bioequivalence studies. Bioequivalence studies have been performed with both strengths because the active substances quantitatively proportional composition of the different strengths is not the same. According to the information in the SmPC Sitagliptin/Metformin hydrochloride Mylan should be given with meals to reduce the gastrointestinal adverse reactions associated with metformin. Therefore, bioequivalence studies have been performed under both fasted and fed conditions.

Bioequivalence studies undertaken:

1. Study No. C18136: A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film - coated tablets 50mg/1000mg and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50mg/1000mg in normal healthy adult human subjects under fasting conditions;

2. Study No. C18137: A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin hydrochloride film - coated tablets 50mg/1000mg and Janumet (Sitagliptin/Metformin hydrochloride) film-coated tablets 50mg/1000mg in normal healthy adult human subjects under fed conditions;

3. Study No. SIME-1-19123: A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film - coated tablets 50mg/850mg and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50mg/850mg in normal healthy adult human subjects under fasting conditions.

4. Study No. SIME-1-19124: A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film - coated tablets 50mg/850mg and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50mg/850mg in normal healthy adult human subjects under fed conditions.

Study No. C18136

Study design

A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film-coated tablets 50mg/1000mg of Mylan Laboratories Limited, India and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50 mg /1000mg of Merck Sharp & Dohme BV Waarderweg 39 2031 BN Haarlem Netherlands in normal healthy adult human subjects under fasting conditions with a screening period of 21 days prior to the volunteers participation in the study.

Pharmacokinetic Variables

The primary pharmacokinetic variables were C_{max} , and AUC_{0-t} .

The secondary pharmacokinetic variables were AUC_{0-inf}, t_{max}, $t_{1/2}$, $K_{el,}$ $(AUC_{0-t}/AUC_{0-inf})*100$.

Statistical methods

For pharmacokinetic and statistical analysis actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix WinNonlin version 8.0.for Sitagliptin and Metformin.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin were subjected to Analysis of Variance (ANOVA). ANOVA model included terms for Sequence, Formulation and Period and Subject (Sequence) as fixed effects. The sequence effect was tested using the Subject (Sequence) effect as an error term.

Two one-sided test for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations were calculated, for ln-transformed data of C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

The power of a test to detect 20% difference between test and reference products were computed and reported for Sitagliptin and Metformin.

Ratio of least squares means of test and reference products were computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Ratio analysis was reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Intra-Subject variability was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Determination of sample size

The maximum observed intra-subject variability for Sitagliptin among primary pharmacokinetic parameters (C_{max}) was found to be 16%. Hence, considering the CV of 16% the following estimates were considered for the computation of sample size:

T/R ratio (expected between) = 90-111.1%

Intra-Subject C.V (%) = 16%

Significance Level = 5%

Power = >90%

Bioequivalence Limit=80-125.00%

Based on the above estimate, a sample size of 34 subjects were sufficient to establish bioequivalence between formulations with adequate power. However, considering the dropouts, a sample size of 36 subjects were considered for the study.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of the test product (A) with that of the reference product (B) under fasting conditions were concluded if the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptable range of 80.00 % – 125.00% for ln-transformed pharmacokinetic parameters of C_{max} and AUC_{0-t} for Sitagliptin and Metformin.

Results

Table 1: Pharmacokinetic parameters for sitagliptin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (hr.ng/mL)	1769.664 ± 443.7090	1722.363 ± 400.2367
$AUC_{0-\infty}$ (hr.ng/mL)	1849.804 ± 426.5894	1835.908 ± 384.5314
C_{max} (ng/mL)	148.153 ± 23.6878	147.525 ± 24.8218
T_{max}* (hr)	4.50 (0.67 - 6.00)	4.50 (1.67 - 5.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 2: Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (hr.ng/mL)	14974.463 ± 4308.1812	14938.324 ± 4055.7423
$AUC_{0-\infty}$ (hr.ng/mL)	15285.933 ± 4376.0831	15260.133 ± 4112.0777
C_{max} (ng/mL)	1928.102 ± 668.6334	1823.053 ± 532.0777
T_{max}* (hr)	4.00 (1.00 - 5.00)	4.50 (1.33 - 5.0)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 3: Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	102.60	98.32 - 107.08	10.58
C_{max} (ng/mL)	100.74	96.06 - 105.64	11.78

Table 4: Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	100.43	93.82 - 107.50	16.93
C_{max} (ng/mL)	104.87	96.87 - 113.54	19.80

Study No. C18137

Study design

A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin hydrochloride film - coated tablets 50mg/1000mg of Mylan Laboratories Limited, India and Janumet (Sitagliptin/Metformin hydrochloride) film-coated tablets 50 mg /1000mg of Merck Sharp & Dohme BV Waarderweg 39 2031 BN Haarlem Netherlands in normal healthy adult human subjects under fed conditions with a screening period of 21 days prior to the volunteers participation in the study.

Pharmacokinetic Variables

The primary pharmacokinetic variables were C_{max}, and AUC_{0-t}.

The secondary pharmacokinetic variables were AUC_{0-inf}, t_{max}, $t_{1/2}$, K_{el}, $(AUC_{0-t}/AUC_{0-inf})*100$.

Statistical methods

For pharmacokinetic and statistical analysis actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix WinNonlin version 8.0.for Sitagliptin and Metformin.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin were subjected to Analysis of Variance (ANOVA). ANOVA model included terms for Sequence, Formulation and Period and Subject (Sequence) as fixed effects. The sequence effect was tested using the Subject (Sequence) effect as an error term.

Two one-sided test for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations were calculated, for ln-transformed data of C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

The power of a test to detect 20% difference between test and reference products were computed and reported for Sitagliptin and Metformin.

Ratio of least squares means of test and reference products were computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Ratio analysis was reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Intra-Subject variability was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Sitagliptin and Metformin.

Determination of sample size

The maximum observed intra-subject variability for Sitagliptin among primary pharmacokinetic parameters (C_{max}) was found to be 16%. Hence, considering the CV of 16% the following estimates were considered for the computation of sample size:

T/R ratio (expected between) = 90-111.1%

Intra-Subject C.V (%) = 16%

Significance Level = 5%

Power = >90%

Bioequivalence Limit=80-125.00%

Based on the above estimate, a sample size of 34 subjects were sufficient to establish bioequivalence between formulations with adequate power. However, considering the dropouts, a sample size of 36 subjects were considered for the study.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of the test product (A) with that of the reference product (B) under fed conditions were concluded if the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptable range of 80.00 % – 125.00% for ln-transformed pharmacokinetic parameters of C_{max} and AUC_{0-t} for Sitagliptin and Metformin.

Results

Table 5: Pharmacokinetic parameters for sitagliptin (non-transformed values)

Pharmacokinetic parameter	**Test**	**Reference**
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (hr.ng/mL)	1961.490 ± 315.2102	1922.424 ± 310.6720
$AUC_{0-\infty}$ (hr.ng/mL)	2024.850 ± 314.7525	2020.490 ± 293.2180
C_{max} (ng/mL)	135.935 ± 29.5193	141.811 ± 32.3538
T_{max}* (hr)	4.50 (1.67 - 10.00)	4.50 (1.67 - 6.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 6: Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test arithmetic mean ±SD	Reference arithmetic mean ±SD
AUC_{0-t} (hr.ng/mL)	15794.746 ± 3351.9321	15113.010 ± 3033.7897
$AUC_{0-\infty}$ (hr.ng/mL)	16314.818 ± 3510.7140	15600.663 ± 3117.9255
C_{max} (ng/mL)	1704.383 ± 633.5461	1618.085 ± 544.6753
T_{max}* (hr)	5.00 (1.00 - 8.00)	5.00 (1.33 - 6.0)

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max}* time for maximum concentration (* median, range)

Table 7: Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	101.81	97.53 - 106.28	9.98
C_{max} (ng/mL)	95.42	89.34 - 101.91	15.33

Table 8: Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	104.16	100.84 - 107.59	7.51
C_{max} (ng/mL)	103.76	94.60 - 113.81	21.66

Study No. SIME-1-19123

Study design

A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film - coated tablets 50mg/850mg of Mylan Laboratories Limited, India and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50 mg /850mg of Merck Sharp & Dohme BV Waarderweg 39 2031 BN Haarlem Netherlands in normal healthy adult human subjects under fasting conditions, with a screening period of 21 days prior to the volunteers participation in the study.

Pharmacokinetic variables

The primary pharmacokinetic variables were C_{max}, and AUC_{0-t}.

The secondary pharmacokinetic variables were AUC_{0-inf}, t_{max}, $t_{1/2}$, K_{el}, $(AUC_{0-t}/AUC_{0-inf})*100$.

Statistical methods

For pharmacokinetic and statistical analysis actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix WinNonlin version 8.0.for Sitagliptin and Metformin.

The ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Sitagliptin and Metformin were subjected to Analysis of Variance (ANOVA). ANOVA model was included terms for Sequence, formulation and Period and Subject (Sequence) as fixed effects. The sequence effect was tested using the Subject (Sequence) effect as an error term.

Two one-sided test for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations were calculated, for ln-transformed data of Cmax and AUC0-t of Sitagliptin and Metformin.

The power of a test to detect 20% difference between test and reference products were computed and reported for Sitagliptin and Metformin.

Ratio of least squares means of test and reference products were computed for ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Sitagliptin and Metformin.

Ratio analysis was reported for ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Sitagliptin and Metformin.

Intra-Subject variability was computed for ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Sitagliptin and Metformin.

Determination of sample size

Sufficient number of subjects was enrolled to ensure dosing of 36 healthy adult human subjects. The maximum observed intra-subject variability for Sitagliptin among primary pharmacokinetic parameters (Cmax) is found to be 16%. Hence, considering the CV of 16% the following estimates were considered for the computation of sample size:

T/R ratio (expected between) = 90-111.1%

Intra-Subject C.V (%) = 16%

Significance Level = 5%

Power = >90%

Bioequivalence Limit=80-125.00%

Based on the above estimate, a sample size of 34 subjects were sufficient to establish bioequivalence between formulations with adequate power. However, considering the dropouts, a sample size of 36 subjects were considered for the study.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of the test product (T) with that of the reference product (R) under fasting conditions were concluded if the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptable range of 80.00 % – 125.00% for ln-transformed pharmacokinetic parameters of C_{max} and AUC_{0-t} for Sitagliptin and Metformin.

Results

Table 9: Pharmacokinetic parameters for sitagliptin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	arithmetic mean ±SD
AUC_{0-t} (hr.ng/mL)	1816.524 ± 323.2090	1903.055 ± 425.2531
$AUC_{0-\infty}$ (hr.ng/mL)	1874.200 ± 331.5333	1968.920 ± 461.3443
C_{max} (ng/mL)	166.032 ± 38.0903	167.795 ± 38.3956
T_{max}* (hr)	3.33 (1.02 - 6.00)	3.67 (0.67 - 5.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 10: Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	arithmetic mean ±SD
AUC_{0-t} (hr.ng/mL)	16423.364 ± 3657.4450	17147.422 ± 5952.8237
$AUC_{0-\infty}$ (hr.ng/mL)	16707.187 ± 3684.0723	17489.480 ± 6239.0853
C_{max} (ng/mL)	2053.099 ± 523.3709	2016.071 ± 434.8852
T_{max}* (hr)	3.33 (1.00 - 6.00)	4.00 (0.67 - 6.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 11: Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	95.93	91.92 - 100.10	10.72
C_{max} (ng/mL)	98.94	93.38 - 104.82	14.57

Table 12: Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	97.67	92.51 - 103.13	13.71
C_{max} (ng/mL)	101.05	95.40 - 107.04	14.51

Study No. SIME-1-19124

Study design

A randomized, balanced, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study to compare Sitagliptin/Metformin Hydrochloride film - coated tablets 50mg/850mg of Mylan Laboratories Limited, India and Janumet (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50 mg /850mg of Merck Sharp & Dohme BV Waarderweg 39 2031 BN Haarlem Netherlands in normal healthy adult human subjects under fed conditions, with a screening period of 21 days prior to the volunteers participation in the study.

Pharmacokinetic variables

The primary pharmacokinetic variables were C_{max} , and AUC_{0-t} .

The secondary pharmacokinetic variables were AUC_{0-inf}, t_{max}, $t_{1/2}$, $K_{el,}$ $(AUC_{0-t}/AUC_{0-inf})*100$.

Statistical methods

For pharmacokinetic and statistical analysis actual time of blood sample collection was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of Phoenix WinNonlin version 8.0.for Sitagliptin and Metformin.

The ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Sitagliptin and Metformin were subjected to Analysis of Variance (ANOVA). ANOVA model was included terms for Sequence, formulation and Period and Subject (Sequence) as fixed effects. The sequence effect was tested using the Subject (Sequence) effect as an error term.

Two one-sided test for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations were calculated, for ln-transformed data of Cmax and AUC0-t of Sitagliptin and Metformin.

The power of a test to detect 20% difference between test and reference products were computed and reported for Sitagliptin and Metformin.

Ratio of least squares means of test and reference products were computed for ln-transformed pharmacokinetic parameters Cmax and AUC_{0-t} of Sitagliptin and Metformin.

Ratio analysis was reported for ln-transformed pharmacokinetic parameters Cmax and AUC_{0-t} of Sitagliptin and Metformin.

Intra-Subject variability was computed for ln-transformed pharmacokinetic parameters Cmax and AUC_{0-t} of Sitagliptin and Metformin.

Determination of sample size

Sufficient number of subjects was enrolled to ensure dosing of 36 healthy adult human subjects. The maximum observed intra-subject variability for Sitagliptin among primary pharmacokinetic parameters (Cmax) is found to be 16%. Hence, considering the CV of 16% the following estimates were considered for the computation of sample size:

T/R ratio (expected between) = 90-111.1%

Intra-Subject C.V (%) = 16%

Significance Level = 5%

Power = >90%

Bioequivalence Limit=80-125.00%

Based on the above estimate, a sample size of 34 subjects were sufficient to establish bioequivalence between formulations with adequate power. However, considering the dropouts, a sample size of 36 subjects were considered for the study.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of the test product (T) with that of the reference product (R) under fasting conditions were concluded if the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptable range of 80.00 % – 125.00% for ln-transformed pharmacokinetic parameters of C_{max} and AUC_{0-t} for Sitagliptin and Metformin.

Results

Table 13: Pharmacokinetic parameters for sitagliptin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (hr.ng/mL)	1618.956±259.8293	1653.463±246.9316
$AUC_{0-\infty}$ (hr.ng/mL)	1681.579±270.7940	1723.518± 260.3906
C_{max} (ng/mL)	118.771±23.2742	122.908±34.4606
T_{max}* (hr)	3.67(0.67-8.00)	4.25(0.67-8.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 14: Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (hr.ng/mL)	13505.502±3143.5688	13452.582±2951.1422
$AUC_{0-\infty}$ (hr.ng/mL)	13930.357±3278.0231	13903.509±3085.0973
C_{max} (ng/mL)	1358.428±289.9400	1345.37±278.9387
T_{max}* (hr)	4.50(1.00-8.00)	4.50(1.67-8.00)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Pharmacokinetic parameter	Test	Reference
	arithmetic mean ±SD	arithmetic mean ±SD

Table 15: Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	97.86	95.42-100.37	6.15
C_{max} (ng/mL)	97.62	91.08-104.62	16.96

Table 16: Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC_{0-t} (ng.hr/mL)	100.21	97.32-103.19	7.12
C_{max} (ng/mL)	100.70	96.52-105.06	10.33

Pharmacokinetic conclusion

Based on the presented four bioequivalence studies (No.C18136, No.C18137, No.SIME-1-19123 and No.SIME-1-19124) Sitagliptin/Metformin Hydrochloride film-coated tablets 50 mg/1000 mg and 50mg/850mg (Manufactured by Mylan Laboratories Limited, India) are considered bioequivalent with JANUMET (Sitagliptin/Metformin Hydrochloride) film-coated tablets 50 mg/1000mg and 50mg/850mg of Merck Sharp & Dohme.

2.4.2.2. Pharmacodynamics

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

2.4.2.3. Post marketing experience

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

2.4.3. Discussion on clinical aspects

Metformin and Sitagliptin are widely used and well-known active substances. The safety profile and tolerability of Metformin and Sitagliptin are well established.

A justification on the use of an alternative salt (hydrochloride monohydrate) is provided. The Applicant states that there are no pharmacological or toxicological objections against the use of this salt in the proposed indications compared to the phosphate salt and that the different salt of the active substance sitagliptin does not differ significantly in properties with regards to safety and efficacy. The hydrochloride salt also does not differ significantly in physico-chemical properties from the phosphate salt and both salts are highly soluble. The provided justification is considered acceptable.

To support this application, the company has submitted four bioequivalence studies. Bioequivalence studies have been performed with both strengths because the active substances quantitatively proportional

composition of the different strengths is not the same. According to the information in the SmPC Sitagliptin/Metformin should be given with meals to reduce the gastrointestinal adverse reactions associated with metformin. Therefore, bioequivalence studies have been performed under both fasted and fed conditions.

The study designs were considered adequate to evaluate the bioequivalence of these formulations and were 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 formulations of Sitagliptin/Metformin hydrochloride Mylan 850 mg/50 mg film-coated tablets and Sitagliptin/Metformin hydrochloride Mylan 1000 mg/50 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the reference products JANUMET 50mg/850mg sitagliptin/metformin hydrochloride and JANUMET 50mg/1000mg sitagliptin/metformin hydrochloride. The point estimates and their 90% confidence intervals for the parameters AUC0-t and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the four formulations was demonstrated.

Overall, the drug products tested were generally safe and well tolerated by the subjects included in this study. No unexpected safety signals have been reported from the submitted studies. In the bioequivalence studies presented by the applicant all reported adverse events were mild in severity.

The clinical aspects of the Sitagliptin/Metformin hydrochloride Mylan SmPC are in line with the SmPC of the reference product.

2.4.4. Conclusions on clinical aspects

Based on the four bioequivalence studies provided (No.C18136, No.C18137, No.SIME-1-19123 and No.SIME-1-19124) Sitagliptin/Metformin hydrochloride Mylan film-coated tablets 50mg/1000 mg and 50mg/850mg are considered bioequivalent with JANUMET (sitagliptin/metformin Hydrochloride) film-coated tablets 50mg/1000mg and 50mg/850mg.

A benefit/risk ratio comparable to the reference product can therefore be concluded from a clinical viewpoint.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 17:

Summary of safety concerns	
Important identified risks	Lactic acidosis
Important potential risks	Pancreatic cancer
Missing information	Use in pregnancy and during breast-feeding

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application for marketing authorisation of Sitagliptin/Metformin hydrochloride Mylan 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The reference product is Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg marketed by Merck Sharp and Dohme B.V., that was first approved in the European Union on 16 July 2008 via the centralised procedure.

The indications applied for Sitagliptin/Metformin hydrochloride Mylan are the same as those for the reference product Janumet:

For adult patients with type 2 diabetes mellitus:

Sitagliptin/Metformin hydrochloride is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Sitagliptin/Metformin hydrochloride is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Sitagliptin/Metformin hydrochloride is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Sitagliptin/Metformin hydrochloride is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substances were 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 substances; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

To support the application, the Applicant has submitted four bioequivalence studies. Bioequivalence studies have been performed with both strengths because the active substances quantitatively proportional composition of the different strengths is not the same. According to the information in the SmPC Sitagliptin/Metformin hydrochloride Mylan should be given with meals to reduce the gastrointestinal adverse reactions associated with metformin. Therefore, bioequivalence studies have been performed under both fasted and fed conditions.

The studies designs were considered adequate to evaluate the bioequivalence of these formulations and were 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 formulations of Sitagliptin/Metformin hydrochloride Mylan 850 mg/50 mg film-coated tablets and Sitagliptin/Metformin hydrochloride Mylan 1000 mg/50 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the reference products JANUMET 50mg/850mg sitagliptin/metformin hydrochloride and JANUMET 50mg/1000mg sitagliptin/metformin hydrochloride. The point estimates and their 90% confidence intervals for the parameters AUC0-t and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the four formulations was demonstrated.

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. RMP version 0.2 is agreed.

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

4. Recommendations

Outcome

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

> "For adult patients with type 2 diabetes mellitus:
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
>
> Sitagliptin/Metformin hydrochloride Mylan is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
>
> Sitagliptin/Metformin hydrochloride Mylan is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control."

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 marketing authorisation holder (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.