EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2022
EMA/568807/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sitagliptin/Metformin hydrochloride Accord

International non-proprietary name: sitagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/005850/0000

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:	Sitagliptin/Metformin hydrochloride Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	METFORMIN HYDROCHLORIDE / SITAGLIPTIN HYDROCHLORIDE MONOHYDRATE
International Nonproprietary Name/Common Name:	sitagliptin / metformin hydrochloride
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: It 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. It 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. It 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. It 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 / 1000 mg and 50 mg / 850 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PE/PVDC/alu) and blister (alu/alu)
Package size(s):	10 tablets, 168 tablets, 196 tablets, 200 tablets, 28 tablets, 30 tablets, 56 tablets and 84 tablets

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List of abbreviations

API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BDL	Below the limit of detection
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File
DMF	Dimethylformamide
DoE	Design of experiments
DOM	Date of manufacture
DSC	Differential scanning Calorimetry
EC	European Commission
ECD	Electrochemical detection
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FID	Flame ionisation detection
FT-IR	Fourrier transmission infra red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infra-red
IU	International Units
KF	Karl Fischer
LDPE	Low density polyethylene
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass spectroscopy
ND	Not detected
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PDA	Photo diode array
PDE	Permitted Daily Exposure
PE	Polyethylene
PVC	Polyvinyl chloride
PVdC	Polyvinyl dichloride

Ph.Eur.	European Pharmacopoeia
QL	Quantitation limit
QOS	Quality Overall Summary
QTPP	Quality target product profile
RH	Relative Humidity
RMS	Reference member state
RRt	Relative retention time
Rt	Retention time
RT	Room temperature
SAL	Sterility assurance level
SEM	Scanning electron microscopy
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TLC	Thin layer chromatography
TGA	Thermo-Gravimetric Analysis
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
UV	Ultraviolet
XR(P)D	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 27 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sitagliptin/Metformin hydrochloride Accord, 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 29 January 2021.

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:
>
> It 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.
>
> It 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.
>
> It 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.
>
> It 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 10 years in the EEA:

- Product name, strength, pharmaceutical form: Janumet 50mg/850mg and 50mg/1000mg, film-coated tablet
- 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 50mg/850mg and 50mg/1000mg, film-coated tablet
- 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 50mg/850mg and 50mg/1000mg, film-coated tablet
- 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): 61620, 61720

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:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	27 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 January 2022
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	28 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	19 April 2022
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	4 May 2022
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 Accord on	19 May 2022

2. Scientific discussion

2.1. Introduction

The product is Sitagliptin/Metformin hydrochloride Accord, 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The application for marketing authorisation is submitted as 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 (EMEA/H/C/000861).

Sitagliptin/Metformin hydrochloride Accord combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin, a dipeptidyl peptidase 4 (DPP 4) inhibitor, and metformin hydrochloride, a member of the biguanide class. 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 high efficiency in reducing fasting and postprandial blood glucose and lowering glycosylated haemoglobin in patients. The hypoglycaemic 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 dose of antihyperglycaemic therapy with sitagliptin/metformin hydrochloride should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin. Sitagliptin/metformin is given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

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

For adult patients with type 2 diabetes mellitus:
It 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.
It 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.
It 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.
It 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 (E460), calcium hydrogen phosphate, croscarmellose sodium (E468), magnesium stearate (E470b), povidone and sodium laurilsulfate

Film coating: poly(vinyl alcohol), macrogol, talc (E553b), titanium dioxide (E171), red iron oxide (E172) and black iron oxide (E172) (For 50/1000 mg strength only)

The product is available in PVC/PE/PVDC-aluminium blisters and Alu-Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance - Sitagliptin Hydrochloride Monohydrate

2.2.2.1. General Information

The chemical name of sitagliptin hydrochloride monohydrate is (3*R*)-3-amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one hydrochloride monohydrate corresponding to the molecular formula $C_{16}H_{18}ClF_6N_5O_2$. It has a relative molecular mass of 461.8 g/mol and the following structure:

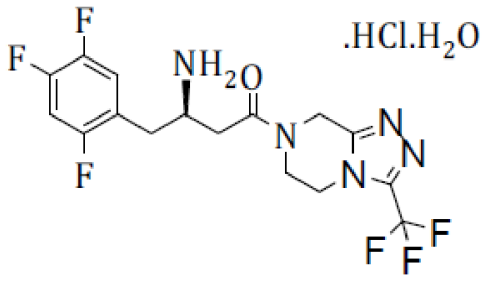

Figure 1: active substance structure

The chemical structure of sitagliptin hydrochloride monohydrate was confirmed by a combination of elemental analyses, UV spectroscopy, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The solid-state properties of the active substance were measured by XRD.

Sitagliptin hydrochloride monohydrate is a white to almost-white powder, slightly hygroscopic and freely soluble in aqueous media across the physiological pH range.

Sitagliptin hydrochloride monohydrate exhibits stereoisomerism due to the presence of one chiral center which is introduced selectively in the synthetic process. The (*R*)-enantiomer of the active substance is synthesised. Enantiopurity is routinely controlled by a chiral HPLC method in the active substance specification.

It has been demonstrated through XRD analysis, that the manufacturing process consistently produces the same crystal structure and polymorphic form, and the polymorphic form is stable during storage.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

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

Sitagliptin hydrochloride monohydrate is synthesized in 8-10 main steps (depending on the intermediate manufacturer) using three 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 characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. During the procedure, a major objection was raised on the restricted part of the ASMF in relation to impurity control in one of the starting materials which was addressed in a satisfactory way by the ASMF Holder. A further major objection was raised on the applicant's part of the ASMF due to the detection of an unexpected impurity in active substance from one intermediate manufacturing site. Further work revealed that with the GC method used, the unexpected impurity co-eluded with another impurity which is routinely controlled in the active substance specification. An optimised method was developed, in which the two peaks elude separately. Active substance samples were tested with the improved method and the unexpected impurity was not detected. The tested batches included samples of active substance manufactured with intermediate from the two different intermediate manufacturers, respectively.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in a transparent low-density polyethylene (LDPE) bag with strip seal and then in another transparent LDPE bag with strip seal followed by a triple laminated sunlight barrier bag (TLSB) with heat seal. These bags are further packed in HDPE containers. The primary packaging material complies with the EC directive EC 10/2011 as amended and with monograph Ph. Eur 3.1.3. for polyolefins.

2.2.2.3. Specification

The active substance specification used by finished product manufacturer includes tests for: description (visual), solubility (Ph. Eur.), identity (IR, enantiomeric purity and test for chloride), hydrochloric acid content (potentiometry), water content (KF), sulfated ash (Ph. Eur), related substances (HPLC), enantiomeric purity (HPLC), assay (HPLC), residual solvents (GC), benzene content (GC), polymorphic form (PXRD) and particle size (laser diffraction).

The specification is identical to the specification used by the active substance manufacturer and in line with the Ph. Eur. Monograph for sitagliptin phosphate, where applicable, with the additional test for particle size, polymorphic form and residual solvents.

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. 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.

2.2.2.4. Stability

Stability data from three production-scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH

guidelines were provided. Samples were tested for description, identification, water content, related substances, enantiomeric purity, assay and polymorph. 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 parameters remained within specifications.

The active substance was also exposed to stressed conditions. The active substance is sensitive to degradation under acidic, basic and oxidative conditions. No changes were observed under thermal stress and high humidity. In photostability studies, degradation was observed in solution but not in the solid state.

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 and at temperatures not exceeding 25°C (excursions permitted between 15°C and 30°C). The packaging protects the active substance from light during storage.

2.2.3. Active substance - Metformin Hydrochloride

2.2.3.1. General Information

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride corresponding to the molecular formula $C_4H_{12}ClN_5$. It has a molecular mass of 165.6 and the following structure:

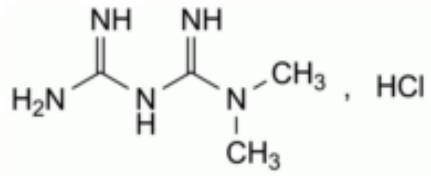

Figure 2: active substance structure

Metformin hydrochloride is a white or almost white crystalline powder, non-hygroscopic and freely soluble in aqueous media across the physiological pH range.

Metformin hydrochloride has a non - chiral molecular structure.

Metformin hydrochloride exhibits polymorphism. It has been demonstrated that the manufacturing process consistently produces the same polymorph.

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.

2.2.3.2. Manufacture, characterisation and process controls

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

2.2.3.3. Specification

The active substance specification includes pharmacopoeial tests (as used by finished product manufacturer) for description (visual), solubility (Ph. Eur.), identity (IR, test for chlorides) (Ph. Eur.), appearance of solution (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), related substances

(HPLC) and assay (titrimetry). Additional tests are carried out by the finished product manufacturer for residual solvents (GC) and particle size (laser diffraction).

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

Additional specifications have been set for residual solvents and particle size. Non-compendial methods have been adequately validated and described according to ICH Q2. Limits for particle size were set in line with batches used to manufacture finished product for the bioequivalence studies.

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.

2.2.3.4. Stability

No re-test period is stated on the CEP and therefore results of stability studies in support of the retest period have been provided.

Stability data from 16 batches of active substance (out of which 12 were production-scale batches) from the proposed manufacturer stored in the intended commercial packaging for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for description, identity, appearance of solution, loss on drying, related substances and 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 under long term and accelerated conditions.

The active substance was also exposed to stressed conditions. The active substance is sensitive to degradation under basic and oxidative conditions and minor changes were seen under acetic conditions. No changes were observed under thermal stress and high humidity. In photostability studies, degradation was observed in solution but not in the solid state.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months (as assigned by the finished product manufacturer) when stored at ambient temperature in the proposed, well-closed container.

2.2.4. Finished medicinal product

2.2.4.1. 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: pink coloured, capsule shaped, film-coated tablet debossed, with 'SM2' on one side and plain on other side. Length: 20.10 to 20.40 mm and Width: 9.80 to 10.10 mm.
- 50 mg / 1000 mg: red coloured, capsule shaped, film-coated tablet debossed with 'SM3' on one side and plain on other side. Length: 21.30 to 21.60 mm and Width: 10.40 to 10.70 mm.

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. A different salt of an active substance is considered to be the same active substance, if does not differ significantly in properties with regard to safety and efficacy (see non-clinical/clinical aspects).

The excipients were selected based on the excipients used in the reference product with certain differences. Calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate are used for the generic but are not used in the reference product. Sodium stearyl fumarate is used in the reference product, but not in the generic. For the film-coat, the same individual components are used except for iron oxide black which is used for the 50 mg/ 850 mg reference product, but not included in the Opadry selected for the generic.

Compatibility of each excipient with both active substances was overall sufficiently demonstrated under accelerated conditions (40ºC, 75% RH). 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.

For metformin hydrochloride, two polymorphic forms are known and for sitagliptin hydrochloride monohydrate one singular crystalline form. XRPD analysis was used to study if any changes in polymorphic form occur during tablet manufacturing and/or storage. No change in polymorphic form was observed and the data presented was considered satisfactory.

The quality target product profile (QTTP) was derived from chemical and physical properties of the two active substances, from the characteristics of the reference product and the reference product label and from the intended patient population.

Critical quality attributes (CQAs) were identified, and assay, uniformity of dosage units, dissolution and related substances are identified as the subset of CQAs that have the potential to be impacted by formulation and/or process variables. Risk assessment was used throughout development to identify potentially high-risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated after development to capture the reduced level of risk based on improved product and process understanding.

Design of experiments was used in formulation development studies. The two tablet strengths are not dose proportional. The dose of sitagliptin remains quantitatively the same while the portion of metformin varies across the two strengths.

The development of the dissolution method is described in sufficient detail and the selected method was appropriately justified. The discriminatory power of the dissolution method was investigated. Sufficient information on the discriminatory power of the dissolution method was provided considering also that the tablets are for immediate release and the active substances are freely soluble.

Bioequivalence with the reference product was demonstrated in two studies (see clinical aspects). In addition, comparative *in vitro* dissolution studies were conducted. Dissolution profiles were very similar for the generic and the reference product.

A risk assessment of the overall finished product manufacturing process was performed to identify the high risk steps that may affect the CQAs of the final finished product. A risk assessment was conducted to identify potentially high risk process variables which could impact the finished product CQAs. This

method of identifying process variables for further study was applied in each process step risk assessment. Previous experience with these process steps was used to determine the degree of risk associated with each process step and its potential to impact the CQAs of the finished product. Further risk assessment was performed subsequently on each high and/or medium risk process step to identify which process variables may potentially impact the intermediate CQAs. Evaluation of all possible process variables that could potentially impact the quality attributes of the output material of any given process step was not feasible therefore; some of the variables were set constant based on proven acceptable ranges of development and current understanding. Following the experiments conducted roller pressure and fluid intake may impact the tablet dissolution, under or over-blending may impact tablets assay and uniformity of dosage units, turret speed, hardness (compression force) and compression run time were identified as critical process parameters and as scale dependent parameters. Therefore, these parameters will be evaluated during scale up batch execution.

The primary packaging is PVC/PE/PVDC-aluminium blisters or Alu-Alu blisters. 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.

2.2.4.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process, along with in-process tests, consists of six main steps: 1) intra-granular stage, 2) extra granular stage, 3) sifting and blending, 4) compression, 5) coating, and 6) 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. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.4.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description (visual), identification (HPLC, HPLC by PDA, titanium dioxide, iron dioxide), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), water content (KF), related substances (HPLC), *N*-nitroso dimethylamine (NDMA, GC-MS/MS) and microbiological quality (Ph. Eur.).

Related substances are limited in line with ICH Q3B.

Following the first round of assessment, a question was raised in relation to the proposed limits for total impurities, both at release and at shelf life. Limits were considered too wide for total impurities related to sitagliptin, for total impurities related to metformin hydrochloride and also for the total of both. The CHMP requested to tighten the limits in line with process capabilities, product behaviour and batch data at release and from stability studies. Reference was also made to the limit for total impurities in the Ph. Eur. Monograph for sitagliptin phosphate. Following the responses received, the issue was upgraded to a Major Objection. Following that, the applicant provided satisfactory responses to resolve the Major Objection and relevant limits were tightened to acceptable limits.

Following the first round of assessment, a question was also raised on the proposed assay limits for sitagliptin and metformin hydrochloride and the proposed widening of limits at shelf life. Following the responses received, the issue was upgraded to a Major Objection in the List of Outstanding issues as the provided data was insufficient to justify the proposed limits at release and the widening of limits

proposed for the shelf-life specification. The applicant then provided satisfactory responses to resolve the Major Objection.

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 3 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 dimethyl amine as an impurity and is known to be susceptible to formation of NDMA during formulation. NDMA is routinely controlled in the finished product. Numerous batches of both strengths were tested when packaged in the proposed primary container and in all instances the results were below the limit of quantification (0.01 ppm).

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.

2.2.4.4. Stability of the product

Stability data from 3 production-scale batches of finished product of each strength stored for up to 18 months under long term conditions (25 ºC / 60% RH), 12 months at intermediate conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in both of the primary packaging proposed for marketing, respectively.

Samples were tested for description, water content, dissolution, assay, related substances and microbiological quality. The analytical procedures used are stability indicating. Under long-term conditions, no significant changes were observed for either strength and for either packaging. Under accelerated conditions, no significant changes were observed for either strength packaged in Alu/Alu blisters. In the PVC/PE/PVDC blister packaging, an increase of sitagliptin-related impurities was observed, but results remained within the specification limits.

In addition, samples were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In solution, degradation is seen for both APIs, but no changes were observed for the tablet (solid), including under directly exposed conditions.

Forced degradation studies were also conducted. It was observed, that sitagliptin is sensitive to oxidative, acidic, and basic conditions. Metformin is sensitive to oxidative and basic conditions, while only minor

changes were seen under acetic conditions. Under thermal stress and high humidity, no changes were seen for both sitagliptin and metformin.

Based on available stability data, the proposed shelf-life of 2 years and the storage condition 'Store below 30°C' as stated in the SmPC (section 6.3) are acceptable.

2.2.4.5. 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. Regarding the active substance, a Major Objection was raised during the procedure in relation to control of impurities in one of the starting materials used to manufacture the active substance. A further Major Objection was raised due to the detection of an unexpected impurity in active substance from one intermediate manufacturing site. Satisfactory responses were received during the procedure to address and resolve both these Major Objections. Two questions related to the proposed limits for total impurities and assay in the finished product specifications were upgraded to Major Objections during the procedure, but additional responses received were satisfactory to resolve both Major Objections.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. 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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin and metformin are well known. As sitagliptin and metformin are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

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.

A summary of the literature with regards to non-clinical data of sitagliptin and justifications that the different salt of the active substance sitagliptin does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Sitagliptin/Metformin hydrochloride Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all sitagliptin and metformin hydrochloride containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview is adequate. The non-clinical sections of the SmPC are in line with the reference text, Janumet film-coated tablets, Merck Sharp & Dohme B.V., CP product, EMEA/H/C/000861.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Sitagliptin/Metformin hydrochloride Accord and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

There are no objections to approval of Sitagliptin/Metformin hydrochloride Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film coated tablets containing sitagliptin/metformin hydrochloride. To support the marketing authorisation application the applicant conducted two bioequivalence study with [cross-over / parallel] design under 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 as well as the Guideline on Bioanalytical method validation EMEA/CHMP/EWP/192217/09.

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

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.

Tabular overview of clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies as follows

Study 61620	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover oral bioequivalence study of Sitagliptin and Metformin hydrochloride 50 mg/850 mg film coated tablets, comparing with that of Janumet 50 mg/850 mg film-coated tablets (Sitagliptin and Metformin hydrochloride) of Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands in healthy, adult, human subjects under fed conditions.
Study 61720	An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover oral bioequivalence study of Sitagliptin and Metformin hydrochloride 50 mg/1000 mg film coated tablets, comparing with that of Janumet 50 mg/1000 mg film-coated tablets (Sitagliptin and Metformin hydrochloride) of Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands in healthy, adult, human subjects under fed conditions.

The bioequivalence studies are done on both strengths applied for (50mg/850 mg and 50mg/1000mg) and no biowaiver is therefore requested.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 61620: An open label, An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover oral bioequivalence study of Sitagliptin and Metformin hydrochloride 50 mg/850 mg film coated tablets, comparing with that of Janumet 50 mg/850 mg film-coated tablets (Sitagliptin and Metformin hydrochloride) of Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands, in healthy, adult, human subjects under fed conditions.

Methods

- **Study design**

The study was an open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two sitagliptin/metformin 50mg/850mg film-coated tablet formulations in 36 healthy adult subjects under fed conditions (high-fat/high-calorie meal). The study was conducted under standardised conditions. Sitagliptin and metformin were measured in human plasma using a validated LC/MS/MS method. Dosing was done in groups.

- **Test and reference products**

Product Characteristics	Test Product	Reference Product
Name	Sitagliptin and Metformin hydrochloride 50 mg/850 mg film-coated tablets	Janumet 50 mg/850 mg film-coated tablets
Active substance	Sitagliptin / Metformin	Sitagliptin / Metformin

MAH	-		Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Netherlands.	
Batch number	E2002211		S013456	
Measured content(s) (% of label claim)	Sitagliptin	99.8 %	Sitagliptin	97.8 %
	Metformin	97.7 %	Metformin	98.5 %
Batch size (Biobatch)	211,765 Tablets			
Commercial batch size	211,765 Tablets			
Manufacturing date	May 2020		-	
Expiry date (Retest date)	Apr 2022		10-2020	
Member State where the reference product is purchased from	-		Netherlands	

- **Population(s) studied**

36 healthy adult male subjects (20-42 years old, BMI 18.6 - 29.9 kg/m2) of Asian race were enrolled and randomized. Five (05) subjects (no. 04, 13, 18, 22 and 25) dropped out. 31 subjects completed both periods and were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The method validation reports (MV0400, Version 00, dated 21/10/2019, Addendum-I signed on 22/10/2019, Addendum-II signed on 27/11/2019, Addendum-III signed on 04/08/2020 and Addendum-IV signed on 28/10/2020) have been provided for the method of sitagliptin and metformin.

A validated LC-MS/MS method by solid-phase extraction was used to determine sitagliptin and metformin concentrations in K_2EDTA human plasma. The internal standards were sitagliptin-D4 hydrochloride and metformin-D6 HCl. Certificates of analysis are provided for the analytes and the internal standards.

The calibration curve range and quality control concentrations during study sample analysis were:

Sitagliptin:

Calibration range: 3.0204-1501.2 ng/ml

QC concentrations (ng/ml): 8.7258 (LQC), 93.826 (AQC-II), 187.65 (AQC-I), 525.63 (MQC) and 1140.2 (HQC).

Metformin:

Calibration range: 10.063-5001.3 ng/mL

QC concentrations (ng/ml): 29.079 (LQC), 312.68 (AQC-II), 625.36 (AQC-I), 1751.7 (MQC) and 3799.8 (HQC).

Accuracy and precision of QC samples obtained during analysis of subject samples is shown below:

Sitagliptin

Inter-run precision: 1.5 – 2.8%
Inter-run accuracy: 97.2 – 100.2%

Metformin:

Inter-run precision: 1.9 – 3.1%
Inter-run accuracy: 98.6 – 100.3%

A total of 1733 samples were analysed. A total of 02 samples (0.12%) were reanalysed for sitagliptin due to incomplete analysis, inconsistent internal standard response and poor chromatography and a total of 01 sample (0.06%) was reanalysed for metformin due to incomplete analysis.

For incurred sample reanalysis 140 samples were run for sitagliptin and 140 samples for metformin. A total of 100% of samples were found to be within a variation of 20% from the mean value for sitagliptin and 99.3% for metformin. Long term stability of the analytes in matrix at -70±15°C and -20±10°C was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

- **Pharmacokinetic variables**

The primary pharmacokinetic parameters for this study were AUC_{0-t} and C_{max}, and the secondary pharmacokinetic parameters were $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, Residual area, T_{max}, $T_{1/2}$ and K_{el} for both sitagliptin and metformin, respectively.

The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach. Actual sampling times were used for calculation of the PK parameters, except for pre-dose samples. The PK analysis software used was Phoenix WinNonlin Software Version 8.3.

- **Statistical methods**

PROC GLM of SAS Studio 3.6 (Basic Edition) (SAS Institute Inc., USA) was employed for statistical analysis. ANOVA was performed on ln transformed pharmacokinetic parameters for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The model included group, sequence, sequence*group, period (group), treatment, treatment*group and subject (sequence*group) as fixed effects. The ln-transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) of Sitagliptin and Metformin were analyzed using an ANOVA model at alpha 0.05.

Bioequivalence criteria:

90% confidence interval for the difference of the least-square means of the logarithmic transformed values of C_{max} and AUC_t at 5% level of significance should be between 80.00% and 125.00% to meet bioequivalence criteria for Sitagliptin and Metformin.

Results

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

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$	1945.536	356.834	1930.756	276.735
$AUC_{(0-\infty)}$	2029.734	378.014	2009.526	289.282
C_{max}	154.81	43.880	147.13	41.339
T_{max}*	4.50 (1.33 - 6.50)	-	4.50 (1.33 - 6.50)	-
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. Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	Arithmetic mean	SD
$AUC_{(0-t)}$	16267.143	4432.583	16026.094	3340.903
$AUC_{(0-\infty)}$	16433.747	4398.623	16152.004	3327.260
C_{max}	1645.1	487.56	1535.6	410.27
T_{max}*	4.50 (1.33-8.00)	-	5.50 (1.33 - 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 3. Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intra subject CV (%)
$AUC_{(0-t)}$	100.36	97.99 - 102.79	5.5
$AUC_{(0-\infty)}$	100.57	98.19 - 103.01	5.5
C_{max}	104.92	97.63 - 112.75	16.5

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intra subject CV (%)
$AUC_{(0-t)}$	100.21	95.82 - 104.80	10.2
$AUC_{(0-\infty)}$	100.54	96.25 - 105.03	10.0
C_{max}	106.13	99.97 - 112.67	13.7

The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00% for both sitagliptin and metformin, respectively.

- **Safety data**

A total of 06 post-dose adverse events were reported by 05 of the total 36 subjects included in the study. Two subjects reported vomiting and two subjects reported headache, furthermore, one subject (no. 16) had abnormal laboratory values (decreased haemoglobin and decreased HCT) at check-out of period-II and was lost to follow up post study.

01 adverse events were observed in relation to the test product and 03 adverse events were observed in relation to the reference product. The severity of the adverse events were mild or moderate. No serious adverse events or deaths were reported during this study.

Two subjects were withdrawn from the study for safety reasons (due to vomiting). Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Study 61720: An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover oral bioequivalence study of Sitagliptin and Metformin hydrochloride 50 mg/1000 mg film coated tablets, comparing with that of Janumet 50 mg/1000 mg film-coated tablets (Sitagliptin and Metformin hydrochloride) of Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands in healthy, adult, human subjects under fed conditions.

Methods

- **Study design**

The study was an open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two sitagliptin/metformin 50mg/1000mg film-coated tablet formulations in 36 healthy adult subjects under fed conditions. The study was conducted under standardised conditions. Sitagliptin and metformin were measured in human plasma using a validated LC/MS/MS method.

- **Test and reference products**

The reference product is Janumet 50mg/850mg film-coated tablets by Merck Sharp & Dohme B.V., registered since 16-07-2008. Further information about the test and reference products used in study 61720 are enclosed in below table.

Table 5.

Product Characteristics	**Test Product**		**Reference Product**	
Name	Sitagliptin and Metformin hydrochloride 50 mg/1000 mg film coated tablets		Janumet 50 mg/1000 mg film-coated tablets	
Active substance	Sitagliptin / Metformin		Sitagliptin / Metformin	
MAH	-		Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Netherlands.	
Batch number	E2002411		S022335	
Measured content(s) (% of label claim)	Sitagliptin	98.1 %	Sitagliptin	97.5 %
	Metformin	98.3 %	Metformin	99.0 %
Batch size (Biobatch)	180,000 Tablets			
Commercial batch size	180,000 Tablets			

Manufacturing date	Jun 2020	-
Expiry date (Retest date)	May 2022	01-2021
Member State where the reference product is purchased from	-	Netherlands

- **Population(s) studied**

36 healthy adult male subjects (19-43 years old, BMI 19.1 - 28.4 kg/m^2) of Asian race were enrolled and randomized. Five (05) subjects (no. 13, 19, 20, 24 and 36) dropped out (see details below). 31 subjects completed both periods and were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The method validation reports (MV0400, Version 00, dated 21/10/2019, Addendum-I signed on 22/10/2019, Addendum-II signed on 27/11/2019, Addendum-III signed on 04/08/2020 and Addendum-IV signed on 28/10/2020) have been provided for the method of sitagliptin and metformin.

A validated LC-MS/MS method by solid-phase extraction was used to determine sitagliptin and metformin concentrations in K_2EDTA human plasma. The internal standards were Sitagliptin-D4 hydrochloride and Metformin-D6 HCl. Certificates of analysis are provided for the analytes and the internal standards.

The calibration curve range and quality control concentrations during study sample analysis were:

Sitagliptin:

Calibration range: 3.0204-1501.2 ng/ml

QC concentrations (ng/ml): 8.7258 (LQC), 93.826 (AQC-II), 187.65 (AQC-I), 525.63 (MQC) and 1140.2 (HQC).

Metformin:

Calibration range: 10.063-5001.3 ng/mL

QC concentrations (ng/ml): 29.079 (LQC), 312.68 (AQC-II), 625.36 (AQC-I), 1751.7 (MQC) and 3799.8 (HQC).

Accuracy and precision of QC samples obtained during analysis of subject samples is shown below:

Sitagliptin

Inter-run precision: 1.9 – 4.7%

Inter-run accuracy: 97.4 – 100.3%

Metformin

Inter-run precision: 1.8 – 7.1%

Inter-run accuracy: 98.5 – 100.8%

A total of 1735 samples were analysed. A total of 02 samples (0.12%) were reanalysed for sitagliptin due to inconsistent internal standard response and poor chromatography and a total of 01 sample (0.06%) was reanalysed for metformin due to inconsistent internal standard response.

For incurred sample reanalysis 140 samples were run for sitagliptin and 140 samples for metformin. A total of 98.6% of samples were found to be within a variation of 20% from the mean value for sitagliptin and 100% for metformin. The maximum study sample storage period from the first blood draw (23/09/2020) to last sample analysis (20/10/2020) is 28 days, which is covered by the validated long-term stability.

- **Pharmacokinetic variables**

The primary pharmacokinetic parameters for this study were AUC_{0-t} and C_{max}, and the secondary pharmacokinetic parameters were $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, Residual area, T_{max}, $T_{1/2}$ and K_{el} for both sitagliptin and metformin, respectively.

The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach. Actual sampling times were used for calculation of the PK parameters, except for pre-dose samples. The PK analysis software used was Phoenix WinNonlin Software Version 8.3.

- **Statistical methods**

PROC GLM of SAS Studio 3.6 (Basic Edition) (SAS Institute Inc., USA) was employed for statistical analysis. ANOVA was performed on ln transformed pharmacokinetic parameters for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The ln-transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) of Sitagliptin and Metformin were analyzed using an ANOVA model at alpha 0.05. The model included sequence, treatment, period and subject (sequence) as fixed effects. The significance of the sequence effect at alpha 0.10 was calculated using the subject nested within the sequence as the error term.

Bioequivalence criteria:

90% confidence interval for the difference of the least-square means of the logarithmic transformed values of C_{max} and AUC_t at 5% level of significance should be between 80.00% and 125.00% to meet bioequivalence criteria for Sitagliptin and Metformin.

Results

Table 6. Pharmacokinetic parameters for sitagliptin (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$	1935.818	282.611	1953.113	250.068
$AUC_{(0-\infty)}$	2019.815	305.003	2037.836	271.677
C_{max}	169.13	38.258	169.34	38.891
T_{max}*	3.67 (1.00 - 8.00)	-	3.67 (1.33 - 6.50)	-
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. Pharmacokinetic parameters for metformin (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	**SD**	**Arithmetic mean**	**SD**
$AUC_{(0-t)}$	16766.931	3787.917	16962.950	3574.762
$AUC_{(0-\infty)}$	16905.747	3769.842	17094.379	3571.867
C_{max}	1856.6	443.11	1835.8	381.62
T_{max}*	4.50 (1.33-7.00)	-	4.50 (1.00 - 7.00)	-
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 8. Statistical analysis for sitagliptin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intra subject CV (%)
$AUC_{(0-t)}$	99.12	97.53- 100.73	3.7
$AUC_{(0-\infty)}$	99.15	97.64- 100.67	3.5
C_{max}	99.73	93.61- 106.25	14.7

Table 9. Statistical analysis for metformin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intra subject CV (%)
$AUC_{(0-t)}$	98.20	94.28- 102.27	9.4
$AUC_{(0-\infty)}$	98.27	94.39- 102.30	9.3
C_{max}	99.77	93.27- 106.73	15.6

The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00% for both sitagliptin and metformin.

- **Safety data**

A total of 18 post-dose adverse events were reported by 13 of the total 36 subjects included in the study, including itching (05), vomiting (04), nausea (03), headache (02), abdominal pain (01), gastric reflux (01), dyspepsia (01), diarrhoea (01). 09 adverse events were observed in relation to the test product and 09 adverse events were observed in relation to the reference product. The severity of the adverse events was mild or moderate. No serious adverse events or deaths were reported during this study.

Four subjects were withdrawn from the study for safety reasons (due to vomiting). Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

- ***Pharmacokinetic conclusion***

Based on the presented bioequivalence studies Sitagliptin/Metformin hydrochloride Accord is considered bioequivalent with Janumet.

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

Two bioequivalence studies, one for each strength of the applied sitagliptin/metformin fixed dose combination product (50 mg/850 mg and 50 mg/1000 mg) were submitted. Both studies were of a standardized, randomized, 2-way, cross-over design and conducted under fed state in line with the Guideline on the investigation of bioequivalence and the method of administration recommendations of the reference products SmPC. The analysis was done on the parent analytes, sitagliptin and metformin, with a validated LC/MS/MS method, according to the Guideline on bioanalytical method validation.

Results of both bioequivalence studies were within the conventional acceptance range of 80.00%-125.00% CI.

In response to D120 List of Questions the applicant provided a detailed list of all regulatory inspection done at QPS Bioserve India Private Limited, Hyderabad, since 2005 and their outcomes. The site has been inspected several times with the most recent ones in 2020 (WHO), US FDA (2019) and UK MHRA (2019). No critical observations were made during these inspections. No inspection of the submitted bioequivalence studies is needed.

2.4.4. Conclusions on clinical aspects

The application contains an adequate review of published clinical data and based on the presented bioequivalence studies Sitagliptin/Metformin hydrochloride Accord is considered bioequivalent with Janumet.

A summary of the literature with regard to clinical data of sitagliptin/metformin and justification that the different salt of the active substance of sitagliptin (hydrochloride monohydrate vs phosphate monohydrate) does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Approval is recommended from the clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Lactic acidosis
Important potential risks	• Pancreatic cancer
Missing information	• Exposure during pregnancy and lactation

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 1.0 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. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of sitagliptin hydrochloride monohydrate and metformin hydrochloride film coated tablets. The reference product Janumet is indicated in the treatment of type 2 diabetes mellitus, for adult patients:

- 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.
- 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.
- 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.
- 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 substance 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.

Two bioequivalence studies, one for each strength of the applied sitagliptin/metformin fixed dose combination product (50mg/850 mg and 50mg/1000mg), form the pivotal basis with a standardized, randomized, 2-way, cross-over design. Both studies were conducted under fed state in line with the Guideline on the investigation of bioequivalence. 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 Sitagliptin/Metformin hydrochloride Accord met the protocol-defined criteria for bioequivalence when compared with the reference product Janumet. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

This application contains a different salt of the active substance sitagliptin (hydrochloride monohydrate vs phosphate monohydrate). A summary of the literature with regard to non-clinical and clinical data of Sitagliptin/Metformin hydrochloride Accord and justifications that the different salt of sitagliptin does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical/clinical studies were not considered necessary.

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.

A benefit/risk ratio comparable to the reference product can therefore 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 Accord is favourable in the following indication:

> For adult patients with type 2 diabetes mellitus:
>
> It 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.
>
> It 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.
>
> It 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.
>
> It 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.