14 October 2021
EMA/611380/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Sitagliptin SUN

International non-proprietary name: sitagliptin fumarate

Procedure No. EMEA/H/C/005741/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| API | Active Pharmaceutical Ingredient |
| Alu | Aluminium |
| ASMF | Active Substance Master File = Drug Master File |
| BCS | Biopharmaceutics Classification System |
| CFU | Colony Forming Units |
| CoA | Certificate of Analysis |
| CQA | Critical Quality Attribute |
| DECFB | Desiccant embedded Cold form blister |
| EEA | European Economic Area |
| FTIR | Fourier-transform infrared spectroscopy |
| GC | Gas Chromatography |
| GMP | Good Manufacturing Practice |
| HDPE | High Density Polyethylene |
| HPLC | High performance liquid chromatography |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration |
| IR | Infrared |
| KF | Karl Fischer titration |
| LDPE | Low density polyethylene |
| LOD | Limit of Detection |
| LOQ | Limit of Quantitation |
| LoQ | List of Questions |
| NLT | Not less than |
| NMT | Not More Than |
| PA | Polyamide |
| PE | Polyethylene |
| Ph. Eur. | European Pharmacopoeia |
| ppm | parts per million |
| PSD | Particle Size Distribution |
| QbD | Quality by Design |
| RH | Relative Humidity |
| rpm | rotations per minute |
| RRT | Relative retention time |

| | |
|---|---|
| RSD | Relative standard deviation |
| SmPC | Summary of Product Characteristics |
| TAMC | Total Aerobic Microbial Count |
| TYMC | Total Combined Yeasts/Moulds Count |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | U.S. Pharmacopoeia |
| UV | Ultraviolet |
| XR(P)D | X-Ray (Powder) Diffraction |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 9 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Sitagliptin SUN, 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 17 September 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 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 SUN is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin SUN is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin 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 Januvia 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: Januvia film-coated tablets 25 mg, 50 mg and 100 mg
- Marketing authorisation holder: Merck Sharp and Dohme B.V.
- Date of authorisation: 21/03/2007
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/07/383

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

- Product name, strength, pharmaceutical form: Januvia film-coated tablets 25 mg, 50 mg and 100 mg
- Marketing authorisation holder: Merck Sharp and Dohme B.V.
- Date of authorisation: 21/03/2007
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/383

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: Januvia film-coated tablets 100 mg
- Marketing authorisation holder: Merck Sharp and Dohme B.V.
- Date of authorisation: 21/03/2007
- Marketing authorisation granted by:
  - Union
- Bioavailability study number(s): BE/20/206

## *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: Alar Irs

The Rapporteur appointed by the PRAC was: Menno van der Elst

| | |
|---|---|
| The application was received by the EMA on | 9 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 | 15 February 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 24 February 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | N/A |
| 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 | 22 May 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 | 28 June 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 8 July 2021 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 22 July 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on | 13 September 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 | 29 September 2021 |
| The CHMP Rapporteur circulated the CHMP and PRAC Updated Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 7 October 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 SUN on | 14 October 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

The application for marketing authorisation of Sitagliptin SUN 25 mg, 50 mg and 100 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 Januvia 25 mg, 50 mg and 100 mg film-coated tablets, marketed by Merck Sharp and Dohme B.V., that was first approved in the European Union on 21/03/2007 via the centralised procedure (EU/1/07/383).

Sitagliptin SUN contains 'sitagliptin fumarate', a different salt form as compared to the reference product Januvia that contains the salt 'sitagliptin phosphate monohydrate'. According to Article 10(2) of Directive 2001/83/EC (as amended), "*The different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and /or efficacy."* Sitagliptin fumarate and sitagliptin phosphate do not significantly differ with regard to safety and efficacy and as such, can be considered to be the same active substance.

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiological regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent. When blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin secretion is markedly enhanced as glucose rises above normal concentrations. GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose-dependent mechanism is unlike the mechanism seen with sulfonylureas where insulin is released even when glucose levels are low, which can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP-4 with nanomolar potency (IC50 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP-9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

The indications applied for Sitagliptin SUN are the same as those for the reference product Januvia:

> "For adult patients with type 2 diabetes mellitus, Sitagliptin SUN is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin SUN is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control."

Sitagliptin SUN tablets are administered orally and can be taken with or without food. The tablets are not to be crushed or broken before administration. The recommended starting dose of sitagliptin is 100 mg. If sitagliptin is taken with a sulphonylurea or insulin, the dose of the sulphonylurea or insulin may need to be lowered to reduce the risk of hypoglycaemia (low blood sugar levels). In patients with moderately or severely reduced kidney function the dose of sitagliptin should be reduced.

Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Currently available data are described in sections 4.8, 5.1, and 5.2 of the SmPC. Sitagliptin has not been studied in paediatric patients under 10 years of age.

Serious side effects reported with sitagliptin include pancreatitis and hypersensitivity. Hypoglycaemia has been reported in combination with a sulphonylurea and with insulin. For the full list of all side effects reported, see the SmPC.

Sitagliptin must not be used in people who are hypersensitive (allergic) to sitagliptin or any of the other ingredients and in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as film-coated tablets containing 25 mg, 50 mg and 100 mg of sitagliptin. The product contains the sitagliptin fumarate salt.

Other ingredients are:

Tablet core: calcium hydrogen phosphate (E341), crospovidone type A (E1202), hydrogenated castor oil, glycerol dibehenate and magnesium stearate (E470b).

Film coating: hypromellose 2910/5 (E464), titanium dioxide (E171), macrogol 6000 (E1521), talc (E553b), red iron oxide (E172) and yellow iron oxide (E172).

The product is available in PA/Alu/PE + desiccant/HDPE/Alu blisters and in HDPE bottles as described in section 6.5 of the SmPC.

## 2.2.2. Active substance

### *2.2.2.1. General Information*

The chemical name of sitagliptin fumarate is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3- (trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine fumarate corresponding to the molecular formula $C_{20}H_{19}F_6N_5O_5$. It has a relative molecular mass of 523.38 g/mol and the following structure:

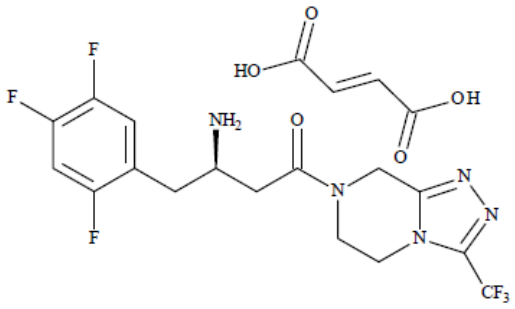


**Figure 1: active substance structure**

The chemical structure of sitagliptin fumarate was elucidated by a combination of nuclear magnetic resonance spectroscopy ($^1$H NMR), carbon nuclear magnetic resonance spectroscopy ($^{13}$C NMR), mass spectrometry (MS), infra-red spectroscopy and UV spectroscopy.

Sitagliptin fumarate is a white to off-white crystalline powder, it is non-hygroscopic and soluble in water. Sitagliptin fumarate has good solubility across the physiological pH range.

Sitagliptin exhibits stereoisomerism due to the presence of one chiral centre. The *R*-enantiomer is used as active substance and the undesired *S*-enantiomer is routinely controlled by chiral HPLC in the active substance specification.

Polymorphism has been observed for sitagliptin. The polymorphic form of sitagliptin fumarate active substance was measured by X-ray powder diffraction (XRPD). It has been demonstrated that the active substance manufacturer consistently produces polymorphic form-I. The polymorphic form is controlled in the active substance *via* testing by XRPD.

### *2.2.2.2. Manufacture, characterisation and process controls*

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. The ASMF holder is the single supplier of sitagliptin fumarate. A number of sites are involved in the manufacturing process.

Sitagliptin fumarate is synthesised in 10 main steps using two well defined starting materials with acceptable specifications.

During the procedure, a major objection was raised in relation to the designation of a starting material as initially proposed. In response, a re-defined starting material was proposed, which was considered acceptable and resolved the major objection.

A further major objection was raised in relation to the designation and control of a second starting material. In response, a satisfactory control strategy in line with ICH M7 (option 3) was presented and the fate of impurities originating from the starting material has been discussed. All potential impurities that can form during manufacture of the starting material are included in the starting material specification. Based on the additional information provided, this active substance starting material for sitagliptin fumarate is acceptable.

The specifications and control methods for starting materials, intermediates and reagents have been presented. Adequate in-process controls are applied during the synthesis. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities are well discussed and characterised. The origin and fate of each impurity has been addressed. The limits of specified, unspecified and total impurities comply with the relevant ICH guidelines. The analytical results provided confirm the ability of the process to remove impurities to the very low limits specified.

The information regarding potential genotoxic impurities has been presented in the restricted part of ASMF as it is related to the detailed description of the manufacturing process. The ASMF holder has adequately justified that these impurities do not need to be controlled in the final active substance.

The proposed limits of residual solvents are in line with the ICH Q3C requirements and their presence and fate have been sufficiently addressed. Solvents used in the final three steps of the active substance synthesis are also controlled in the active substance specification.

Changes introduced during development of the commercial manufacturing process have been presented in sufficient detail and have been justified.

The active substance is packaged in a transparent inner LDPE bag, which is twisted and tied. The bag is then inserted into a black LDPE bag and heat sealed. Both bags are further packed into an outer bag and the triple bag is then placed in a HDPE carboy under nitrogen blanketing. Satisfactory information has been provided on the packaging material which complies with Ph. Eur. requirements and EC 10/2011 as amended.

#### *2.2.2.3. Specification*

The active substance specification includes tests for: description (visual), solubility (Ph. Eur.), identity (HPLC, IR), water content (Ph. Eur.), residue on ignition (sulphated ash), impurities (HPLC), chiral purity (chiral HPLC), assay (HPLC), content of fumaric acid (HPLC), residual solvents (GC), tapped bulk density (Ph. Eur.) and particle size (XRPD).

Limits for impurities have been set in line with ICH requirements and based on batch data. Limits for residual solvents have been set in line with ICH Q3C requirements.

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 three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

#### *2.2.2.4. Stability*

Stability data from five production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 18 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. All stability indicating parameters of the active substance specification have been tested (description, identification by IR, water content, related substances, impurities, chiral purity and assay). The analytical methods used were the same as for release and are stability indicating. Under long term conditions, all results remained within the acceptance limits and no trends were observed. Levels of impurities remained low under long term storage conditions. Under accelerated conditions, an increase in impurities was observed, but all the results remained well within specification.

Photostability testing following the ICH guideline Q1B was performed. Samples were analysed for description, assay, fumaric acid content, chiral purity and related substances. The data showed no significant change in the tested parameters. It can therefore be concluded that sitagliptin fumarate is photostable.

Results from forced degradation studies showed no significant increase in the level of impurities under peroxide, photolytic and humidity conditions indicating that the active substance is stable under these conditions. However, degradation was observed under acid, alkali and thermal degradation conditions demonstrating that the active substance is not stable under these conditions.

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 24 months when stored in well-closed containers between 2°C to 8°C.

### 2.2.3. Finished medicinal product

#### *2.2.3.1. Description of the product and Pharmaceutical development*

The finished product is presented as film-coated tablets containing 25 mg, 50 mg and 100 mg of sitagliptin (as fumarate salt) as active substance. The different tablet strengths are appropriately differentiated by their colour, size and debossing.

| Drug Product | Strength | Description |
|---|---|---|
| Sitagliptin tablets | 25 mg | Light pink colour, round film coated tablets debossed with F1 on one side and plain on the other side[#]. |
| | 50 mg | Light beige colour, round film coated tablets debossed with F2 on one side and plain on the other side[##]. |
| | 100 mg | Beige colour, round film coated tablets debossed with F3 on one side and plain on the other side[###]. |

The objective of formulation development was to design a generic immediate release solid dosage formulation containing the active substance sitagliptin, which is similar and bioequivalent to the reference product Januvia. The qualitative formulation was developed in line with the reference product and the quantity of each excipient was determined based on optimisation studies.

Sitagliptin Sun film-coated tablets contain a different salt form of the active substance sitagliptin in comparison to the reference product (fumarate salt *vs* phosphate salt used in Januvia). While fumaric

acid is a weak organic acid, phosphoric acid is a strong inorganic acid. Fumarate salts of active substances have been widely used in approved oral medicinal products and the active substance sitagliptin in the fumarate form is expected to exhibit the same pharmacokinetics, pharmacodynamics and toxicity as the active substance in the reference product.

As the active substance sitagliptin fumarate exhibits polymorphism, the stability of the polymorphic form produced was investigated at 40 °C/75 % RH over six months. Tablets packed in blisters and HDPE bottles were studied. No change in polymorphic form was observed, demonstrating that the polymorphic form of the active substance does not change during manufacture or storage of the finished product.

Based on the results of excipient compatibility studies, excipients for the core tablet with similar functional use compared to the reference product formulation were selected.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for the film-coating material which is controlled according to in-house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The quality target profile for the product contains suitable targets and justifications for this generic oral dosage form and is based on the properties of the active substance, information on the reference product and consideration of the label and intended patient population of the reference product. All finished product critical quality attributes were identified with low risk.

Bioequivalence was studied between Sitagliptin SUN and the reference product Januvia. The bioequivalence study was conducted by comparing Sitagliptin SUN 100 mg tablets with Januvia 100 mg tablets. The 100 mg Sitagliptin SUN batch used for the bioequivalence study was manufactured according to the commercial manufacturing process and has the same composition as the commercial 100 mg formulation. In addition to the study, comparative *in-vitro* dissolution studies were conducted Dissolution was compared across the physiological pH range of 1.2 to 6.8 (0.1 M HCl pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8) and in purified water. The finished product is rapidly dissolving (i.e. more than 85% within 15 min) at all tested pH conditions and the dissolution of Sitagliptin SUN and the reference product was found to be comparable. To support a biowaiver of strength, dissolution rates for the biobatch 100 mg tablet were compared with the dissolutions rates for the lower strengths tablets (25 mg and 50 mg) and found to be comparable. The three different strengths of the medicinal product are dose proportional and manufactured using a common blend and using the same process. A biowaiver can be accepted for the additional strengths as the requirements of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are met. In addition, dissolution of the batch used for bioequivalence studies was compared with two other 100 mg batches in QC media to show batch-to-batch consistency.

Development studies for the dissolution method to be used for quality control (QC) were carried out using the highest strength tablet as the worst-case scenario. Similar dissolution was observed with different apparatus, dissolution media, volume and rpm.

The discriminatory nature of the dissolution method has been evaluated. It can be concluded, that the suitability of the test conditions for routine testing has been demonstrated using batches with different quality attributes. Sufficient information has been provided to demonstrate that due to the high solubility of the active substance the dissolution method could not be developed further to increase the discriminatory power. The selected QC dissolution test method is acceptable. As an additional measure to control the quality of the finished product, a disintegration test has been included in the specification for sitagliptin tablets.

Direct compression was chosen as an appropriate process. A risk assessment of the overall drug product manufacturing process was performed to identify the level of risk that may affect the CQAs of the final drug product. In different manufacturing steps CQAs were identified but all risks were assigned as medium (or low). Further experiments were performed subsequently for each medium risk process step to identify the suitable process parameter range. After detailed experimentation, the initial manufacturing process risk assessment was updated, and the risks were reduced to an acceptable level (low) and critical process parameters were defined.

An in-process hold time study was performed on blend, core tablets and coated tablets. Description, assay, related substances, water, disintegration (for core and coated tablets only), dissolution (for core and coated tablets only) and microbial purity were studied. No significant change was observed However, no hold time is proposed. This is acceptable taking into account that the finished product is a solid oral dosage form and in line with the guideline "Note for Guidance on Start of Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96)" as the maximum holding time of 30 days has not been exceeded.

The primary packaging is either PA/Alu/PE + desiccant/HDPE/Alu blisters or HDPE bottles. 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.

#### *2.2.3.2. Manufacture of the product and process controls*

The manufacturing process consists of eight main steps: dispensing, sifting, blending, lubrication, compression, preparation of film coating dispersion and film-coating. The process is considered to be a standard manufacturing process.

The critical steps in the manufacture of Sitagliptin 25 mg, 50 mg and 100 mg film-coated tablets are blending, compression and packaging and during these manufacturing steps in-process controls are performed.

Major steps of the manufacturing process have been validated on three commercial-scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. An acceptable validation protocol has been submitted and the process will be fully validated before commercialisation. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

#### *2.2.3.1. Product specification*

The finished product release specifications include appropriate tests for this kind of dosage form: description (in-house), identification (HPLC, IR, colour test), uniformity of dosage units (Ph. Eur.), average weight (in-house), water content (KF), disintegration time (Ph. Eur), dissolution (HPLC), related substances (HPLC), assay (HPLC), microbial purity (Ph. Eur.) and residual solvents (GC).

The proposed specification is in line with ICH Q6A and the Ph. Eur. monographs for Pharmaceutical Preparations and Tablets. It is noted that a Ph. Eur. monograph for sitagliptin tablets is available. However, as this monograph concerns the product containing a different sitagliptin salt (phosphate monohydrate) than that used in Sitagliptin SUN tablets (fumarate), the monograph is not applicable for the product in this application.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been 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). Based on the information provided, it is accepted that no risk was identified of the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

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 three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

#### *2.2.3.2. Stability of the product*

Stability data from three batches of finished product 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 representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Stability studies were conducted for the blister pack and for the HDPE bottles.

Samples were tested for description, water content, dissolution, related substances, assay, disintegration time and microbial purity. The analytical procedures used are stability indicating.

All results were within the proposed shelf-life specifications and no significant changes have been observed.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed.

In-use stability studies

In-use stability studies have been performed on two batches of Sitagliptin tablets 25 mg, and 100 mg packed in HDPE bottles with 33mm/38mm child resistant closure with seal liner, which is proposed for marketing. The bottles contained 90 tablets. The in-use stability studies have been performed at 25°C/60%RH for 180 days and all results remained within specification limits. Hence there is no need to specify an in-use shelf life.

Start of Shelf-life of Finished Dosage Form

Calculation of the product's shelf-life complies with guidance on the start of shelf-life of the finished dosage form (CPMP/QWP/072/96/EMEA/CVMP/453/01).

Based on available stability data, the proposed shelf-life of 2 years as stated in the SmPC (section 6.3) is acceptable. As stated in the SmPC (section 6.4), the product does not require any special storage conditions.

#### *2.2.3.3. Adventitious agents*

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

### 2.2.4. 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. Two major objections related to designation and control of the active substance starting materials have been resolved during the procedure. Bioequivalence has been demonstrated between Sitagliptin SUN 100 mg film-coated tablet and the reference product, Januvia 100 mg film-coated tablet, and biowaivers have been accepted for the other strengths (25 mg and 50 mg). 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.

### 2.2.5. 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.

### 2.2.6. Recommendations for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

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

According to Article 10(2) of Directive 2001/83/EC (as amended), "*The different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy*." There are no specific concerns identified with regard to the new salt form used in the finished product.

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

### 2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Sitagliptin SUN manufactured by Sun Pharmaceutical Industries Europe B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all sitagliptin fumarate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

### 2.3.3. Discussion on non-clinical aspects

In single dose toxicity studies conducted with sitagliptin in rats, the highest non-lethal dose was 271 and 182 times the human exposure based on AUC, respectively.

In repeat-dose toxicity studies, the maximum non-lethal dose was 750 mg/kg/day for mice (approximately 80 times the human exposure based on AUC), 500 mg/kg/day for rats (48 times the

human exposure based on AUC), and ≥ 50 mg/kg/day for dogs (≥ 22 times the human exposure based on AUC). Liver toxicity was seen in both mice and rats.

Sitagliptin showed no genotoxic effects in *in vitro* or *in vivo* assays on mutagenicity (Ames test), direct DNA damage, or clastogenicity.

In the two-year mouse carcinogenicity study, there were no treatment-related increases in tumour incidence in any organ at all tested doses (50, 125, 250, 500 mg/kg/day). In the two-year rat carcinogenicity study, there was a treatment-related increase in hepatic tumours at systemic exposure levels 58-times the human exposure levels.

Sitagliptin did not affect male or female fertility in rats at the limit dose of 1000 mg/kg/day. In rabbits, maternal toxicity was seen at 500 mg/kg/day (decreased food consumption, no faeces). Sitagliptin was shown to cross the placental barrier with foetal exposure values 45 to 80% those in the dam and was also concentrated in milk about 4-fold compared to plasma in rats.

The series of toxicology studies have demonstrated the toxicologic and safety profile of fumarate in a variety of animal species. Fumarate was found to be non-genotoxic, non-carcinogenic in animal and human, and did not cause reproductive toxicities. Available non-clinical data provides evidence to support the safety of fumarate in human. As maximum daily dose of sitagliptin in human is 100 mg, the maximum intake of fumarate through sitagliptin fumarate tablets would be only approximately 28.5 mg/day which is within the acceptable intake.

In conclusion, presented preclinical data provides evidence to support the safety of sitagliptin fumarate in human and no new or unexpected safety concern unlikely to arise due to salt change. The proposed drug product is expected to be safe and well tolerated.

The justification for the lack of full Environmental Risk Assessment is endorsed; the proposed generic product does not lead to an increase of environmental exposure of the active substance.

### 2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Sitagliptin SUN and justifications that the different salt of the active substance does not differ significantly in properties with regard 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.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This is an application for 25 mg, 50 mg and 100 mg film-coated tablets containing sitagliptin fumarate. To support the marketing authorisation application the applicant conducted a bioequivalence study on sitagliptin 100 mg film-coated tablets with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

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 applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of rivaroxaban based on published literature. The SmPC is in line with the

SmPC of the reference product.

***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.

***Exemption***

The Applicant requested a biowaiver for the additional strengths 25 mg and 50 mg film-coated tablets, suggesting that the bioequivalence study results of the 100mg strength can be extended to 25 mg and 50 mg film-coated tablets, according to the general biowaiver requirements [Ref: Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, since the following holds:

a) All the strengths i.e. 25 mg, 50 mg and 100 mg film-coated tablets are manufactured by the same manufacturer i.e. Sun Pharmaceutical Ind. Ltd. using the same manufacturing process;

b) The qualitative composition of the different sitagliptin film-coated tablet strengths is the same;

c) The compositions of the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance(s) is the same for all strengths;

d) The dissolution profiles are similar under identical conditions for the additional strengths compared to the batch used in the bioequivalence study;

e) Sitagliptin demonstrates linear pharmacokinetics: AUC of sitagliptin increases in a dose-proportional manner over the therapeutic dose range.

The rationale for a biowaiver for the 25 mg and 50 mg strengths was accepted.

## 2.4.2. Clinical pharmacology

### *2.4.2.1. Pharmacokinetics*

***Study BE/20/206:*** An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Sitagliptin tablets 100 mg of Sun Pharmaceutical Industries Limited, India with Januvia (Sitagliptin) film coated tablets 100 mg of Merck Sharp & Dohme B.V. in normal, healthy, adult, human subjects under fasting condition.

***Methods***

- **Study design**

Study BE/20/206 was an open-label, bioanalyst-blinded, randomized, single dose, two-period, two-treatment cross-over bioequivalence study in healthy adult subjects under fasting conditions with a wash out period of 9 days between two administrations. In each period single dose of either test or reference product of 100 mg sitagliptin tablets was administered orally.

- **Pharmacokinetic variables**

Primary variables were $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$

Secondary pharmacokinetic parameters determined were $AUC_{\%\ Extrap}$, $T_{max}$, $K_{el}$ and $T_{1/2}$

- **Statistical methods**

The pharmacokinetic parameters for sitagliptin were calculated from the plasma concentration vs. time profile by non-compartmental model. Statistical comparison of the PK of the two formulations was carried out to assess the bioequivalence between test and reference formulations.

Actual time-points of the sample collection are used for the calculation of PK parameters. All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations. Individual AUC parameters were calculated using the linear trapezoidal rule. The log-transformed pharmacokinetic parameters $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ were analyzed using TYPE III sum of square with the main effects of sequence period, formulation, and subjects nested within sequence. The sequence effect was tested at the 10% level of significance using the subjects nested within sequence mean square as the error term. Formulation and period effect were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term.

*Criteria for conclusion of bioequivalence*:

The 90% confidence interval for the ratio of test and reference product averages (least squares means) for pharmacokinetic parameters $C_{max}$ and $AUC_{0-t}$ should be between 80% and 125% for the log-transformed data.

***Results***

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

| Pharmacokinetic parameter | Test N=41 | | Reference N=41 | |
|---|---|---|---|---|
| | **arithmetic mean**<br>**geometric mean** | **SD**<br>**CV%** | **arithmetic mean**<br>**geometric mean** | **SD**<br>**CV%** |
| $AUC_{(0-t)}$<br>(ng*h/mL) | **4467.5348**<br>4395.5034 | ± 840.99769<br>18.82% | **4447.7872**<br>4377.9014 | ± 829.79591<br>18.66% |
| $AUC_{(0-\infty)}$<br>(ng*h/mL) | 4522.5302<br>4449.9514 | ± 848.95063<br>18.77% | 4505.7165<br>4435.3663 | ± 837.89520<br>18.60% |
| $C_{max}$<br>(ng/mL) | **511.961**<br>500.745 | ± 113.1254<br>22.10% | **491.141**<br>475.730 | ± 130.8114<br>26.63% |
| $T_{max}$*<br>(h) | 2.667 | 0.667 - 5.000 | 3.000 | 0.667 - 5.500 |
| $AUC_{0-t}$ | area under the plasma concentration-time curve from time zero to last measurable concentration | | | |
| $AUC_{0-\infty}$ | 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: Statistical analysis for sitagliptin (ln-transformed values)**

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Reference (%) | Confidence Intervals (%) | CV%* |
|---|---|---|---|
| $AUC_{(0-t)}$ | **100.43** | 98.47 – 102.43 | 5.30 |
| $AUC_{(0-\infty)}$ | **100.35** | 98.41 – 102.33 | 5.26 |
| $C_{max}$ | **105.29** | 99.21 – 111.75 | 16.09 |
| * estimated from the Residual Mean Squares | | | |

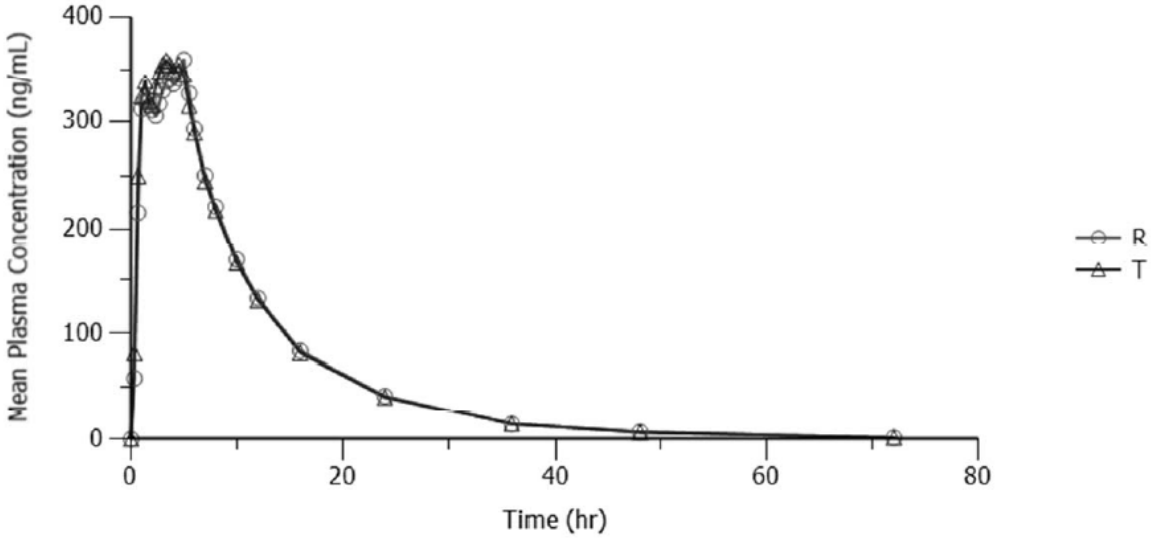


**Figure 2: Mean plasma concentration vs. time curve for sitagliptin after administration of test and reference formulations (100 mg) to healthy subjects (N=41).**

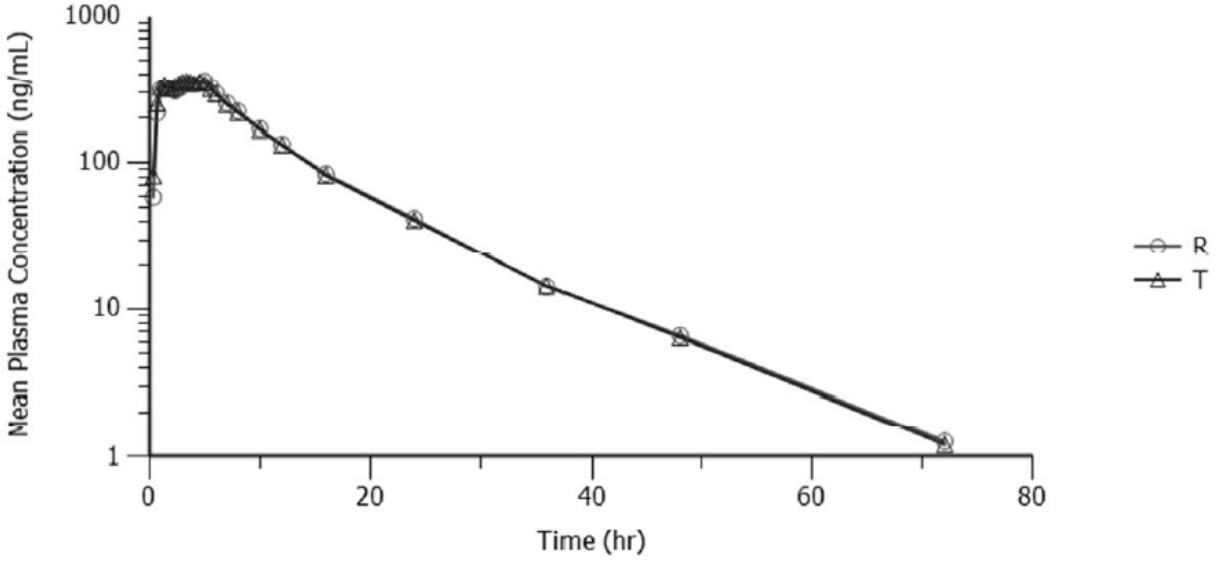


**Figure 3: Semi-logarithmic plot of mean plasma concentration vs. time curve for sitagliptin after administration of test and reference formulations (100 mg) to healthy subjects (N=41).**

Based on the ANOVA results, no significant sequence, period and formulation effects were observed for log-transformed pharmacokinetic parameter $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$.

### *2.4.2.2. Pharmacokinetic conclusion*

Based on the presented bioequivalence study, Sitagliptin SUN 100 mg film-coated tablets by Sun Pharmaceutical Ind. Ltd., Punjab, India are considered bioequivalent with Januvia 100 mg film-coated tablets by Merck Sharp & Dohme Ltd., Cramlington, UK.

The results of the study BE/20/206 with 100 mg formulation can be extrapolated to other strengths 25 mg and 50 mg, according to conditions in the relevant Guidelines.

#### *2.4.2.3. Pharmacodynamics*

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

#### *2.4.2.4. Additional data*

The applicant has performed comparative dissolution studies between test product and reference product bio-batches. The dissolution profiles from those experiments demonstrate similarity between test product and reference formulation in all media, as more than 85% of drug is released within 15 minutes.

#### *2.4.2.5. 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

To support the application, the applicant has submitted a single dose crossover bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Januvia 100 mg film-coated tablets (manufactured Merck Sharp & Dohme Ltd., Cramlington, UK). According to the SmPC of the reference product, the pharmacokinetics of sitagliptin appears linear over the therapeutic dosage range. Sitagliptin can be taken with or without food. Therefore, the selection of the highest dose, 100 mg, to be used in the bioequivalence study under fasting conditions is justified and in accordance to guidelines.

Overall study design is acceptable and in line with pharmacokinetic properties of sitagliptin. The bioequivalence study was conducted under standardised conditions. The sampling period was sufficient, the sampling time schedule and wash-out period were adequate taking into account the $t_{max}$ and elimination half-life of sitagliptin. The sampling schedule reached up to 72 hours, however, the residual area was still evaluated and found to be lower than 20% for all subjects indicating that the duration of sampling was sufficient.

Data regarding the test and reference product were sufficient.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single dose study. The 90% confidence intervals for ln-transformed pharmacokinetic variables $C_{max}$ and $AUC_{0-t}$ were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for sitagliptin were comparable between test and reference product. Both formulations were well tolerated in the study.

Additionally, the applicant has requested a biowaiver for the additional 25 mg and 50 mg strengths. To support the request, a justification and results of comparative dissolution tests have been provided. The in vitro dissolution tests complimentary to the bioequivalence study comparing the in vitro dissolution similarity between biowaiver strengths and the test bio-batch over physiological pH range and in QC media were conducted.

Comparative dissolution profiles demonstrated that the bio-batch and biowaiver strengths of test formulation were essentially similar over the physiological pH range and QC media. More than 85% of sitagliptin was dissolved within 15 minutes in all media, hence the calculation of f2 similarity factors was not necessary. All criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence were fulfilled.

### 2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Sitagliptin SUN 25 mg, 50 mg and 100 mg film-coated tablets are considered bioequivalent with Januvia 25 mg, 50 mg and 100 mg film-coated tablets (by Merck Sharp & Dohme Ltd., Cramlington, UK).

A summary of the literature with regard to clinical data of Sitagliptin SUN 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 clinical studies were not considered necessary. The reference product containing sitagliptin phosphate and the generic product containing sitagliptin fumarate have similar pharmaceutical properties and dissolution profiles, both salts of the active substance dissolved rapidly at all pH levels tested. Sitagliptin is a high solubility compound with complete absorption, i.e. BSC class I.

## *2.5. Risk Management Plan*

### 2.5.1. Safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | Pancreatic cancer |
| Missing information | Exposure during pregnancy and lactation |

### 2.5.2. Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to characterise the important risks and missing information associated with this product.

### 2.5.3. Risk minimisation measures

| **Safety concern** | **Risk minimisation measures** |
|---|---|
| **Pancreatic cancer** | **Routine risk minimisation**<br>No risk minimization proposed<br><br>**Additional risk minimisation measures**<br>Not applicable. |
| **Exposure during pregnancy and lactation** | **Routine risk minimisation**<br>• SPC section 4.6<br>• and Package Leaflet Section 2<br>• Prescription only medicine<br><br>**Additional risk minimisation measures**<br>Not applicable. |

### 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 Januvia 25mg, 50mg and 100mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

# 3. Benefit-risk balance

This application concerns a generic version of sitagliptin film-coated tablets. The reference product Januvia is indicated for:

"For adult patients with type 2 diabetes mellitus, Januvia is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPAR$\gamma$) agonist (i.e. a thiazolidinedione) when use of a PPAR$\gamma$ agonist is appropriate and when diet and exercise plus the PPAR$\gamma$ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these

medicinal products do not provide adequate glycaemic control.

- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin 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.

The bioequivalence study forms the pivotal basis with a two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of sitagliptin tablets 100 mg of Sun Pharmaceutical Industries Limited, India with Januvia (Sitagliptin) film coated tablets 100 mg of Merck Sharp & Dohme B.V. in normal, healthy, adult, human subjects under fasting condition.

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 SUN met the protocol-defined criteria for bioequivalence when compared with the reference product Januvia. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

This application contains a different salt than that of the active substance. A summary of the literature with regard to non-clinical and clinical data of Januvia 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.

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

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

# 4. 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 SUN is favourable in the following indication:

For adult patients with type 2 diabetes mellitus, Sitagliptin SUN is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin SUN is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin 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.