SCIENTIFIC DISCUSSION

1. Introduction

The pathophysiology of Type 2 diabetes mellitus (T2DM) is characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance). This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.
T2DM accounts for approximately 85% to 95% of diabetes cases in developed regions like the European Union. Age and weight are established risk factors for T2DM. The majority of patients with T2DM are overweight or obese. Diet modification and exercise is the first line of treatment for T2DM. Pharmacologic intervention with one oral antidiabetic drug (OAD) is usually the next step in treatment. After 3 to 9 years of OAD monotherapy, patients typically require an additional intervention. The recommended first line treatment is metformin, which restrains hepatic glucose production and decreases peripheral insulin resistance. Sulphonylureas, which are insulin secretagogues, may be used as an alternative to patients intolerant to metformin, or as an addition to metformin. Other second line oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones. Recently the first GLP-1 analogue, exenatide, and the first DPP-4 inhibitors, sitagliptin and vildagliptin, were approved by the CHMP.

Vildagliptin belongs to a new class of oral anti-diabetic drugs and is a selective and reversible inhibitor of Dipeptidyl peptidase 4 (DPP-4), the enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), hormones which significantly contribute to the maintenance of glucose homeostasis.
Metformin is an established first line treatment for T2DM. While the exact mechainsm of action is not fully understood, metformin is thought to act primarily to increase intestinal glucose utilization and enhance hepatic and peripheral insulin sensitivity .

The combination of vildagliptin and metformin is intended for use in patients with T2DM as fixed combination tablets.

The therapeutic indication granted is:
The treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.

The tablets are available in 2 strengths: vildagliptin 50 mg and metformin 850 mg, and vildagliptin 50 mg and metformin 1000 mg. In all cases, the recommended daily dose is 100 mg vildagliptin, allowing a daily dose of 1700 to 2000 mg metformin.

The combination of two classes of antihyperglycaemic agents in one single tablet can improve compliance with treatment, and thus eventually glycaemic control. Currently, no fixed dose combination of a DPP4 inhibitor and metformin is available in Europe.

Vildagliptin (Galvus) has received a positive opinion for granting a marketing authorization on 19 July 2007. Metformin was initially granted national authorisations in the EU from 1959 to 1997. Following a referral to the CPMP under Article 11 of Council Directive 75/319, as amended, a decision on a harmonised SPC for metformin was issued in February 2001. The indication proposed for Eucreas is fully consistent with that already approved for Vildagliptin (Galvus) in combination with metformin.

2. Quality aspects

Introduction

Eucreas is presented as immediate release film-coated tablets containing vildagliptin and metformin hydrochloride as active substances in the strength combination 50 mg/850 mg and 50 mg/1000mg. The other ingredients are hydroxypropyl cellulose and magnesium stearate. The film consists of hypromellose, macrogol, talc, titanium dioxide, purified water and colorants.
The film-coated tablets are marketed in Aluminium/Aluminium (PA/Al/PVC/Al) blister.

Active Substance

Two active substances are used in this fixed combination product, vildagliptin and metformin hydrochloride

Vildagliptin

Its chemical name is (S)-1-[2-(3-Hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2-carbonitrile according to the IUPAC nomenclature.
Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder and no polymorphs or solvates have been identified so far. Vildagliptin is non-hygroscopic and freely soluble in water and polar organic solvents. The above-mentioned active substance has one chiral centre and is used as a single enantiomer (S).

- **Manufacture**

Vildagliptin is synthesised in two reactions steps followed by purification (recrystallisation). The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. Structure elucidation has been performed by elemental analysis, ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, and mass spectroscopy. The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight. The proposed molecular structure was confirmed by X-ray powder diffraction and X-ray single crystal structural analysis.

- **Specification**

The Vildagliptin specifications include tests for appearance (slightly yellowish or slightly greyish powder), particle size (by laser light diffraction), identification (by IR-KBr, IR-ATR and X-ray diffraction), related substances (HPLC and IC), R-enantiomer of vidagliptin (HPLC), residual solvents (Head-space GC), loss on drying (thermogravimetry), sulphated ash, heavy metals, clarity of solution, colour of solution, assay (HPLC) and microbiological limit tests.
It was verified that all specifications reflect the relevant quality attributes of the vildagliptin. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH guidelines.
Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Batch analysis data for the vildagliptin active substance were provided and all results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the vildagliptin. This active substance is not susceptible to degradation under the influence of light and temperature exposure. The results of the long-term and

accelerated studies fulfil the proposed specification and for that reason support the proposed retest period.

Metformin hydrochloride

Metformin hydrochloride's chemical name is 1,1-Dimethylbiguanide monohydrochloride according to the IUPAC nomenclature. This active substance is described in the Ph.Eur. It is a white crystalline powder that is odourless. The compound is freely soluble in water, slightly soluble in ethanol and practically insoluble in acetone, diethylether and dichloromethane. It has a specific crystalline form and has not demonstrated polymorphism or solvates. Particle size does not significantly influence dissolution of metformin hydrochloride, because it is freely soluble in water.

The chemistry, manufacturing and control information on metformin hydrochloride has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued. It was noticed that two additional supplementary tests (Other impurities and residual solvents) were included in the CEP.

Metformin hydrochloride specifications includes tests for appearance (white, crystalline powder), particle size (laser light diffraction), clarity and colour of the solution (Ph.Eur), identification (IR and XRPD), impurities (HPLC), residual solvents (GC), loss on drying (Ph.Eur), sulphated ash (Ph.Eur), heavy metals (Ph.Eur), assay (HPLC) and microbiological limit tests.

The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

Batch analysis data for the metformin hydrochloride drug substances were provided and all batch analysis results comply with the specifications and show consistency from batch to batch.

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the metformin hydrochloride. The re-test period proposed was considered acceptable according to the stability data submitted.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified. Well known excipients were used in the formulation, selected based on their suitability for use in a melt granulation process.

Several tablet strengths of vildagliptin / metformin hydrochloride were developed for Eucreas film-coated tablets and were used either in clinical trials or in stability program. However, only two tablet strengths (50 mg/850 and 50 mg/1000 mg) will be marketed.

The main aim of the applicant was to develop robust final formulation that would be suitable for routine manufacturing at the production scale of film-coated tablets which contain 2 active substances. In this context, different formulation containing slightly different excipients were investigated and optimised. Having investigated different formulations the applicant selected for commercialisation the melt granulation

It was noticed that during the scale up minor changes were made to the formulation. However, it was verified that these changes do not have an impact on the formulation quality and performance.
In order to differentiate the two strengths the colorant used in the film-coating system was slightly different.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing/kneading, melt granulation, compressing and film coating.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that melt granulation step is critical in the manufacturing process.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, identification (TLC and HPLC), mean mass, dissolution (Ph.Eur., HPLC), water (Karl Fischer), degradation products (HPLC), uniformity of dosage units by content uniformity (HPLC), assay (HPLC), microbial limits (Ph Eur).
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. The stability program was based on bracketing between the lowest (1:20) and highest (1:5) ratio of vildagliptin / metformin hydrochloride. For the extremes the following batches were included: three batches are at 25/500 (1:20) and three at 50/250 (1:5). Moreover, one batch each of all the other strengths was also included. It was verified that all batches have been stored at long term and accelerated conditions in the proposed market packaging. One batch each of the extremes was stored under elevated temperature conditions for 3 months and at ICH conditions, another batch each of the extremes was stored under low temperature conditions for 6 months and finally another batch each of the extremes was stored for photostability at ICH conditions.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

Introduction

All pivotal toxicology and safety pharmacology studies were conducted in compliance with Good Laboratory Practices. A facility inspection has been performed of one laboratory site by an EMEA GLP inspection team. The audit did not result in any objections to the use of the audited studies for the safety evaluation.
Non-clinical studies with the combination of vildagliptin and metformin were limited to studies on repeat-dose toxicity and embryo-foetal toxicity.

The non-clinical data relating to vildagliptin consisted mostly of original data from the applicant and was largely identical to the data submitted for the approval of vildagliptin (Galvus).

There is a limited amount of non-clinical data on metformin, and no new original data was submitted. The applicant performed an extensive review of the literature. In the light of the longstanding clinical use of metformin, this was considered to be acceptable by the CHMP.

Pharmacology

Vildagliptin

- Primary pharmacodynamics

In vitro studies
The non-clinical pharmacology program has demonstrated that vildagliptin is a selective and potent inhibitor of DPP-4. The IC_{50} value for inhibition of human DPP-4 is about 3 nM and similar activity was observed with the rat enzyme, demonstrating the lack of species selectivity. Vildagliptin showed some activity at the related enzymes DPP-8 and DPP-9 (Ki values of 506 nM and 65 nM, respectively). Although these values are 253 and 32 times higher than the Ki for DPP-4, activity at C_{max} in humans (2.3 μM) is likely. No assays exist allowing evaluation of DPP-8/DPP-9 inhibition in vivo. The possibility of activity at one or both of these targets is considered a safety concern in relation to the occurrence of skin lesions in monkeys (see below). No, or minimal, inhibition was seen with other related enzymes.

In vivo studies
In vivo pharmacodynamic studies were performed in rats and monkeys. These studies demonstrated the in vivo inhibition of DPP-4 and increased plasma levels of GLP-1. Studies in diabetic rats and in insulin-resistant monkeys demonstrated a glucose-lowering effect of vildagliptin. Chronic effects of vildagliptin were studied in pre-diabetic and insulin-treated diabetic monkeys. Beneficial effects were observed on HbA1c, fasting insulin, fibrinogen and PAI-1.

Vildagliptin increased β-cell mass in neonatal rats, and improved β-cell function in streptozotocin-induced diabetic mice. These data could suggest that vildagliptin has the potential to mitigate the progressive loss of islet function in type 2 diabetes patients.

- Secondary pharmacodynamics

Vildagliptin showed no significant effect on gastric emptying in monkeys. This is in contrast to what has been observed with exogenously-administered GLP-1 and GLP-1 analogues.

As discussed above, activity at the related enzymes DPP-8 and/or DPP-9 can not be excluded at clinical exposures. Concerns related to secondary pharmacology can also arise from the importance of DPP-4 in enzymatic and non-enzymatic functions other than inhibiting the inactivation of GLP-1 and GIP.

DPP-4 (CD26) is present as a cell surface molecule on immune cells and has been characterised as an important costimulatory molecule in immune activation. Although some studies applying DPP-4 inhibitors have suggested a role for the enzyme activity for the immune function, other studies have suggested costimulation to be unrelated to the enzyme activity. The studies performed with vildagliptin and discussed in the dossier support the view that the immune function of CD26 is independent of its enzyme activity.

There are no indications for safety issues related to other DPP-4 substrates than GLP-1 and GIP.

Potential effects on the immune system, resulting in an increased risk for infections and on substance P and neurokinin resulting in an increased risk of angioedema are discussed in the Risk Management Plan. No increased risk has been observed during clinical development for any of these adverse events.

Metformin and Eucreas

No pharmacological studies with metformin or the combination vildagliptin-metformin has been performed by the applicant. The applicant has discussed the pharmacology of metformin based on literature data. While the exact mechanism of the in vivo glucose-lowering by metformin is not fully understood, the primary effects are attributed to a decrease of hepatic glucose production, a delay of intestinal glucose absorption and in increase of glucose disposal in peripheral tissues. All of these effects of metformin are reported in preclinical animal models.

- Safety pharmacology programme

Safety pharmacology studies have been conducted to evaluate neuropharmacological, respiratory and cardiovascular effects of vildagliptin in animals.
Cardiovascular changes were observed in dogs at high doses, occasionally resulting in mortality. Possible mechanisms were examined in an extensive battery of *in vitro* and in *vivo* studies of cardiovascular parameters. These effects are possibly related to inhibition of SCN5A sodium channels which was observed in in vitro studies. Based on dog exposure data (Cmax > 7-fold higher at NOAEL than seen at maximum dose in humans) and the in vitro IC_{50} for sodium channels (365 μM versus clinical Cmax of 2 μM), a clinical effect is unlikely. However, conduction disturbances were further investigated in humans.
No formal safety pharmacology program has been performed with metformin since its development in the 1950s. This was considered acceptable taking into account the extensive accumulated experience with its use since then.

- Pharmacodynamic drug interactions

The effects of combinations of vildagliptin with the rapid-onset insulinotropic agent, nateglinide (Starlix®) and with the insulin sensitizer, pioglitazone (Actos®) were assessed in Zucker fatty rats and resulted in an additive or more than additive effect on several plasma glucose-related parameters.
No specific interaction studies with vildagliptin and metformin had been performed.

Pharmacokinetics

Vildagliptin

Vildagliptin was rapidly absorbed with a high bioavailability in all species. There were no important differences in pharmacokinetic parameters between the tested animal species and humans.

Vildagliptin showed low binding to plasma proteins in all species (<10%). In a whole body autoradiography study in rats, vildagliptin-related radioactivity was widely distributed to most tissues. Drug-related radioactivity was bound to melanin. There was a low passage for drug-related radioactivity across the blood-brain barrier. No radioactivity was detected in any tissue at 48 h post-dose. Studies in pregnant rats and rabbits demonstrated placental transfer of vildagliptin.

The parent compound was one of the major circulating components in all species and all metabolites observed in humans were also found in the animal species. Hydrolysis was the main mechanism of vildagliptin metabolism in all species and exposure to the major metabolites was broadly similar in the rat, dog and human. In humans, the predominant metabolic pathway was hydrolysis at the cyano moiety to form a carboxylic acid metabolite (M20.7/LAY151), accounting for approximately 55% of circulating drug-related material following an oral dose. M20.7 was the main metabolite both in the rat (54%) and the dog (33%). In the rabbit, another hydrolysis product M15.3 was the main metabolite (53%).

Vildagliptin is produced as a pure S-enantiomer. A clinical study showed that chiral conversion *in vivo* is unlikely.

Urinary excretion was the main route in all species except the rat, where equal amounts were excreted with urine and faeces. Milk transfer of vildagliptin and metabolites were demonstrated in the rat, which is therefore mentioned in the SPC section 4.6, with a milk/plasma ratio for total radioactivity of 4.

In vitro studies demonstrated that vildagliptin is unlikely to exhibit a potential for pharmacokinetic drug interactions. Vildagliptin did not inhibit Pgp or any of a series of CYP enzymes. There was no evidence for enzyme induction.

Metformin and Eucreas

Metformin is a highly polar, highly water soluble bi-substituted guanidine derivative that most likely exists as a positively charged molecule under physiological conditions. Consequently, metformin absorption in humans and animals is incomplete. Metformin shows negligible plasma protein binding. Metformin is believed to be a substrate for rodent organic anion transport proteins which may play a part in its distribution to various tissues. Metformin is excreted mainly as unchanged drug in the urine.

Toxicokinetic analysis from toxicity studies with multiple fixed dose combinations of vildagliptin and metformin were conducted in rats and dogs. The results demonstrated the absence of any effect of metformin on vildagliptin, or LAY151 (vildagliptin metabolite) exposure. Exposure to metformin appeared to be slightly increased when coadministered with vildagliptin in some dog and rat studies. Toxicokinetic evaluations were performed in embryo-foetal development studies conducted in rats and rabbits. In general, exposure to vildagliptin and metformin in the foetus was low in both species and metformin exposure was similar in the presence and absence of vildagliptin.

Toxicology

Vildagliptin

- Single dose toxicity

Vildagliptin exhibits low acute toxicity. In mice and rats no toxicological signs were observed after a single oral dose of 2000 mg/kg.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity studies were performed in rats (up to 26 weeks) and dogs (up to 52 weeks). These models are considered relevant, based on the lack of species specificity for the pharmacological activity of vildagliptin, and the similarities in metabolism to humans.

The main toxicological effect noted in rats was the accumulation of clusters of foamy alveolar macrophages in the lung. Similar observations were made in mice. This finding was proposed to be due to an exaggerated pharmacological effect of DPP-4 inhibition in the rat. The clinical relevance of the lung findings in rats cannot be fully excluded. There is a considerable safety margin (5 x human AUC at NOAEL) and the findings are considered of limited importance.

The most consistent toxicological finding in the dog was the appearance of gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhea and at higher doses, faecal blood. These signs were observed at relatively low systemic exposures (observed already at lowest dose representing 2 x human AUC). GI findings were not observed in any other species and according to the applicant no GI disorders have been observed in clinical trials. The CHMP was of the opinion, that these findings are unlikely to be of clinical importance.

- Genotoxicity

The data from genotoxicity studies conducted with vildagliptin in several standard genotoxicity tests do not indicate a genotoxic potential.

- Carcinogenicity

Life-time carcinogenicity studies were performed in mice and rats. No evidence for a carcinogenic potential was observed in the rat. An increased incidence of hemangiosarcomas was observed at the highest dose in female rats while in male rats, the incidence was slightly decreased. Given the mouse findings discussed below, a relation to treatment cannot be fully excluded. In the mouse there was an increased incidence of hemangiosarcomas and mammary carcinoma. The increased incidence of hemangiosarcoma in mice occurred only in organs where this tumour occurs as a relatively common spontaneous finding in the mouse (liver, spleen, uterus etc.). It is suggested that a predisposition to spontaneous hemangiosarcoma at the affected site is needed for vildagliptin to promote an increased incidence. A study in the mouse demonstrated that vildagliptin inhibits VEGF-induced angiogenesis. Based on these mechanistic data the applicant proposes a mechanism whereby inhibition of VEGF-induced angiogenesis over a long period exerts selection pressure in favour of endothelium that proliferates independently of VEGF and hence increases the likelihood of endothelial neoplasia. There was a disproportionate increase in hemangiosarcoma involving the liver in treated male mice at ≥ 250 mg/kg/day. At the same time there was a decreased incidence of hepatocellular carcinoma in male mice. The applicant hypothesizes that hemangiosarcomas may originate within early hepatocellular tumours or preneoplastic lesions followed by obliteration of the hepatocellular tumour and its replacement with the more aggressive hemangiosarcoma. There is a substantial safety margin (exposure margin at NOAEL = 16). It was considered that vildagliptin is likely to act by promoting development of a tumour form that appears commonly mice, and that the data do not suggest an increased risk for hemangiosarcoma development in humans where this tumour form is uncommon. The fact that the incidences of other common spontaneous tumours were not increased by vildagliptin treatment supports the view that a more general tumour promoting effect of vildagliptin is unlikely. The applicant will further study the mechanism for tumour development in the liver of mice, and the findings were considered by the CHMP not to represent a significant risk to humans.

In the case of mammary adenocarcioma, the applicant suggested that tumours noted in the mouse carcinogenicity study are likely the result of an effect on the pituitary-gonadal axis that is unlikely to be of relevance to humans. In mammary tissue from mice treated with vildagliptin for 53 weeks there was a dramatic upregulation of genes related to milk production, such as casein-beta, casein-gamma and lactalbumin, suggesting that hormonally-driven changes are occurring in the mammary gland of mice treated with vildagliptin. The CHMP was of the opinion that these effects are unlikely to be of relevance to humans.

- Reproduction Toxicity

Vildagliptin showed no effects on fertility, reproductive performance or early embryonic development in the rat. Embryo-foetal toxicity was evaluated in rats and rabbits. In the rat, an increased incidence of wavy ribs was observed at ≥ 225 mg/kg/day, in association with reduced maternal body weight parameters. Although classified as a malformation, literature data suggest that wavy ribs in the rat may be reversible. In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted in rabbits at 150 mg/kg/day, in the presence of severe maternal toxicity (including mortality). It is concluded that vildagliptin is not selectively embryotoxic and does not exhibit a teratogenic potential. In the peri- and postnatal toxicity study in rats, maternal toxicity was observed at all doses. Transient decrease in F1 generation body weight and a decreased number of central beam breaks in open-field motor activity tests were observed at ≥ 150 mg/kg/day.

- Local tolerance

Local tolerance of vildagliptin was investigated as part of the intravenous toxicity. No local effects due to vildagliptin were observed in either species. A skin irritation study conducted in rabbits did not indicate any dermal irritant properties.

- Other toxicity studies

Vildagliptin showed no effect on the immune response in KLH-immunised rats. As discussed in the section on Pharmacology, the lack of immunotoxicity supports the view that the immune function of DPP-4/CD26 is independent of its enzymatic activity.

No toxicity studies with metabolites were performed. The main human metabolites were present at similar amounts in the toxicology species. In patients with renal impairment, the exposure to the pharmacologically inactive metabolite LAY151 may be increased up to 6 times. There are no indications for any toxicity related to the metabolite and no further studies are warranted.

Drug impurities requiring toxicological qualification were tested in repeat-dose toxicity and genotoxicity studies with a vildagliptin preparation spiked with the impurities at levels of 2-3%. There were no findings suggesting a change in toxicity profile.

Available data indicate that the administration of DPP-4 inhibitors to monkeys results in dose and duration-dependent increases in necrotic lesions of the tail, digits, ears, nose and scrotum. The mechanism is unknown and such lesions have not been described in humans, rats or dogs. Data from the safety pharmacology study in monkeys suggest that vildagliptin may cause skin lesions in the monkey. A 13-week toxicology in cynomolgus monkeys shows occurrence of necrotic lesions with a lack of safety margin and lack of reversibility at higher doses. The skin lesions are proposed to result from peripheral vasoconstriction.The skin lesions were observed at doses that produced a tachycardic and a prohypertensive action indicating a sympathomimetic effect of vildagliptin at these doses in monkeys.The applicant argues that these findings were related to DPP4 inhibition, and that monkeys are much more sensitive to DPP4 inhibition than humans. The lack of skin lesions with sitagliptin in rhesus monkeys speaks against this proposal suggesting that other factors may be involved in causing the skin lesions result, such as inhibition of DPP8 and or DPP9, the occurrence of which *in vivo* is not known.

Based on mechanistic considerations, no firm conclusion on the relevance of the skin lesions in monkeys for clinical safety can be drawn at this time. The CHMP considered these findings acceptable for a market authorisation, considering the clinical safety documented so far, and appropriate means taken by the applicant to identify any signals in the post-marketing phase. Further studies on the mechanism of skin lesions in the monkeys will be performed as follow-up measures. In addition to describing the findings in SPC section 5.3, a warning is included in section 4.4 with a reference to section 5.3.

Eucreas

Toxicology information for metformin, beyond what is in the product labelling information, is not publicly available. No studies have been performed by the applicant. This is acceptable, given the long clinical experience with metformin.

Repeat-dose toxicity studies up to 13 weeks with the combination vildagliptin and metformin were performed in rats and dogs. No important safety concerns were identified. The effect of the combination of vildagliptin and metformin on embryo-foetal development was studied in rats and rabbits. There was no evidence of teratogenicity in either the rat or rabbit. Adverse effects on the foetus (slight decreases in ossification in rats and increased early resoprtion in rabbits) were associated with metformin-induced maternal toxicity, which included mortality and moribundity, at 10/100 and 100/1000 mg/kg/day vildagliptin/metformin in the rat and rabbit, respectively.

Ecotoxicity/environmental risk assessment

The environmental risk assessment concluded that the concentrations expected to enter the environment are not expected to pose a risk.

4. Clinical aspects

Introduction

The phase III clinical development program consisted of registration studies to support the use of vildagliptin as monotherapy or as combination therapy with other commonly-used antidiabetic drugs (metformin, sulfonylurea, thiazolidinedione, insulin). These were part of an application for Vildagliptin (Galvus), for which the CHMP granted a positive opinion on 19 July 2007. This positive opinion approved the use of Vildagliptin for add-on combination therapy with metformin, sulfonylurea and thiazolidinedione.

The further development of the fixed combination tablets of vildagliptin and metformin led to 4 new pharmacokinetic (PK) studies of the fixed combination tablet as part of the biopharmaceutical development and included:
• 3 cross-over design PK studies in healthy subjects, to assess if the fixed combination tablet is bioequivalent to the free combination of the active components
• 1 cross-over design PK study to assess the effect of food on the absorption of the fixed combination tablet.

The new galenic development did not involve any new clinical pharmacology studies or any new clinical studies. The clinical efficacy and safety data provided for metformin in the current clinical development were further supplemented by the data provided in reviews.

The biopharmaceutical and clinical pharmacology for metformin are well-documented and provided in the product label.

The clinical development program was based on international regulatory guidelines and consultations with health authorities, including EMEA/CPMP Scientific Advice given in November 2003.

There were two important developments within the phase II-III clinical program:

1. The vildagliptin 100 mg dose was initially discontinued by amendment in two phase II dose selection studies and resumed in phase III studies (when the early cardiac findings in dogs at very high exposures were not confirmed in a later clinical cardiac safety study).

2. Additional patients were recruited in five of the key phase III studies in the vildagliptin program to replace those patients whose HbA1c assessments were found to be unreliable and could not be repeated.

The therapeutic indication for Eucreas claimed by the applicant and also finally granted was:
The treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.

GCP

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

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

Pharmacokinetics

A total of 38 clinical pharmacology studies enrolling approximately 1014 subjects have been conducted with vildagliptin to evaluate PK, dose-response, PK/PD relationship, mode of action and potential for drug-drug interactions. Vildagliptin is analyzed in plasma and urine using a specific LC-MS method.

Five biopharmaceutical studies (one relative bioavailability study, one food effect study, and three bioequivalence studies) of vildagliptin/metformin fixed dose combination (FDC) pertinent to this submission were conducted in healthy subjects.

Fixed dose combination
There is good PK rational for the development of the fixed combination under consideration. Metformin and vildagliptin exhibit comparable elimination half-lives and similar subsequent dosing intervals. Also, low potential for drug-drug interaction by enzymatic metabolism is expected.

Three bioequivalence studies, one for each strength, was conducted comparing the rate and extent of absorption of the fixed combination of vildagliptin/metformin FMI tablets (final formulation intended for marketing) with that of a free combination of vildagliptin 50 mg and metformin (Glucophage) tablets used in clinical studies. The studies were open-label, randomized, single-dose, two-treatment, two-period, two-sequence crossover studies. Study medication was taken in a fasting state. Blood samples were collected for 48 h. Vildagliptin and metformin concentration in plasma were simultaneously measured by using LC-MS/MS. Bioequivalence between all three strengths of the fixed combination and the corresponding free combination was demonstrated for both vildagliptin and metformin AUC and C_{max}, using the normal acceptance criteria 0.80-1.25.

The effect of food on the extent and rate of absorption for vildagliptin and metformin components in the fixed combination tablets was investigated using the highest dose (50mg/1000mg). Food had no effect on the rate and extent of absorption of vildagliptin from the fixed combination formulation. Metformin absorption rate was decreased by concomitant food intake resulting in a 26% reduction in C_{max} and delay in t_{max}. Extent of absorption was not significantly affected, with AUC reduced only by 7%. The effect of food on metformin is slightly less than reported previously for Glucophage. The difference in food effect between the fixed combination and Glucophage is not considered clinically relevant.

The potential for PK drug-drug interaction between both components of the fixed combination has been evaluated. No clinically relevant interaction between vildagliptin and metformin was found in the conducted study.

Vildagliptin

- Absorption

Vildagliptin is rapidly absorbed with a median t_{max} of about 1.5 hr after oral dosing and has a mean absolute oral bioavailability of 85.3 ± 10.8 %. An *in vitro* study with Caco-2 cell monolayer suggests that vildagliptin is a substrate of P-gp, with a low affinity, however. The rate of absorption is reduced when vildagliptin final marketing tablets are taken with a high fat meal and there is also a slight reduction of extent of absorption as reflected by an increase in t_{max} from 1.75 h under fasting conditions to 2.5 h after a high fat meal, a 19% decrease in C_{max} and 10% decrease in AUC. These effects are not considered clinically relevant. The mean AUC in patients with Type 2 diabetes mellitus at the therapeutic dose (2160 ± 520 ng·hr/mL, N=71) was comparable to healthy subjects (2275 ± 459 ng·hr/mL, N=150).

- Distribution

The protein binding of vildagliptin to human plasma is low (9.3%). Vildagliptin distributes equally between plasma and red blood cells. The volume of distribution (Vss) is 70.7±16.1 L, indicating distribution to the extravascular tissue compartment.

- Elimination

Vildagliptin is eliminated mainly by metabolism and subsequent urinary excretion of metabolites. After administration of ^{14}C-vildagliptin 100 mg oral solution 85.4±4.4% of the dose was excreted in

urine and 14.8±3.5% in faeces. About 33% of dose was excreted in urine as unchanged vildagliptin after intravenous administration. Mean total plasma clearance (CL) determined after intravenous administration of 25 mg was 40.6±8.97 L/hr and renal clearance (CL_R) 13.0±2.35 L/hr . The mean plasma elimination half-life ($t_{1/2}$) of vildagliptin after oral administration was about 2-3 h. The main metabolic pathway is hydrolysis accounting for about 60% of the dose. Glucuronidation is a minor elimination pathway accounting for 4.4% of the dose and oxidation accounts only for 1.6% of the dose. Multiple tissues can hydrolyse vildagliptin to the major metabolite LAY151. CYP450 isoenzymes are involved in vildagliptin metabolism only to a minor extent. Hence, the potential for interactions with vildagliptin metabolism is very small. The major metabolite LAY151 has no effect on DPP-4 activity, indicating that it is not pharmacologically active. Vildagliptin is an S-enantiomer. Available data suggest that *in vivo* inter-conversion to the D-enantiomer is unlikely.

- Dose proportionality and time dependencies

Dose and time dependency
The pharmacokinetics of vildagliptin is roughly dose proportional. Data on single dose administration of 25-600 mg and multiple dose administration of 25 – 400 mg show that AUC and C_{max} increase slightly more than in proportion to dose, however, the deviation from linearity is minor with a 2.2-fold increase in AUC as the dose is increased 2-fold. No accumulation of vildagliptin is observed following single administration per day of a dose ranging from 25 mg to 200 mg for 10 days. This suggests that the clearance is not time-dependent.

Variability
The inter-subject coefficient of variation for plasma AUC is in the range of 15-20% and in C_{max} about 25% in healthy volunteers after an oral dose. The inter-individual variability in CL/F was 42% in the population PK analysis.

Target population
The applicant has submitted sufficient documentation to demonstrate that vildagliptin pharmacokinetics are similar in diabetic patients when compared to healthy subjects.

- Special populations

Vildagliptin total and renal clearances are decreased in patients with renal impairment. Vildagliptin AUC was increased by 101%, 32%, 134% and 42%, respectively, and AUC of the main metabolite (LAY151) 1.6, 2.4, 5.4 and 6.7 - fold, respectively, in patients with mild, moderate and severe renal impairment, and ESRD. Hepatic impairment has a limited influence of vildagliptin PK, with no effect in mild and moderate hepatic impairment and only a 22% increase in vildagliptin AUC in patients with severe hepatic impairment. AUC of LAY151 increased with decreased hepatic function. There was a 2-fold increase in exposure of LAY151 in severe hepatic impairment. Gender, age, weight and race had no clinically significant effects on vildagliptin exposure. Vildagliptin pharmacokinetics has not been evaluated in children or adolescents.

- Pharmacokinetic interaction studies

CYP450 isoenzymes are involved in vildagliptin metabolism only to a minor extent. Hence, the potential for interactions with vildagliptine metabolism is very small. Vildagliptin is a substrate of P-gp. However, the risk for clinically relevant interactions with inhibitors of P-gp or other transport proteins seems to be low. *In vitro* studies suggested a low potential for interaction with CYP450 isoenzymes. The potential for inhibition of CYP1A2, 2D6, 2C8, 2C9, 2C19, 2E1, 3A4 and P-gp and potential for induction of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, UGT1A1, Pgp and MRP2 has been evaluated *in vitro*. Studies evaluating the potential for inhibition of CYP2B6, UGT1A1 and MRP-2 are lacking.

In vivo interaction studies were conducted with other antidiabetic agents (glyburide, pioglitazone, metformin), some cardiovascular drugs (amlodipine, valsartan, ramipril, simvastatin) and the narrow therapeutic drugs digoxin and warfarin. There were no clinically relevant interactions between

vildagliptin and the studied drugs. A small effect on digoxin renal clearance (19% reduction) might suggest a mild inhibition of P-glycoprotein. However, this is unlikely to be clinically relevant for digoxin or for other P-gp substrates. Simvastatin is a substrate for CYP3A4, S-warfarin is a substrate of CYP2C9 and pioglitazone is a substrate of CYP2C8. Lack of *in vivo* interaction with these substrates support the *in vitro* prediction that vildagliptin is not expected to affect the PK of substrates of CYP3A4, CYP2C9 and CYP2C8.

It can be concluded that the interaction potential of vildagliptin is low.

Metformin

Metformin has an absolute oral bioavailability of 40-60%. The absorption is incomplete and saturable with lower bioavailability at higher doses. Metformin is rapidly distributed and does not bind to plasma protein. No metabolites or conjugates of metformin have been identified, and renal excretion of unchanged metformin is the major elimination pathway. The mean elimination half-life of metformin after oral administration is between 4.0 and 8.7 hours. The elimination is prolonged in patients with renal impairment and correlates with creatinine clearance resulting in increased exposure in patients with renal impairment. For this reason, metformin is contraindicated in patients with renal dysfunction, defined as creatinine clearance <60 ml/min. This is reflected in the SPC in section 4.3, with related warnings in section 4.4.

Pharmacodynamics

- Mechanism of action

Vildagliptin belongs to a new class of oral anti-diabetic drugs and acts as a selective and reversible inhibitor of DPP-4. This enzyme inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). The inhibition of DPP-4 therefore increases the levels of these hormones which is likely to be the most significant contribution to the improvement of glucose homeostasis by vildagliptin.
The pharmacodynamics of metformin is not completely understood, but its main glucose-lowering effect appears to be caused by reduced hepatic glucose output and enhanced peripheral glucose uptake.

- Primary and Secondary pharmacology

In vildagliptin pharmacodynamic studies, a single dose of vildagliptin in patients with T2DM lead to inhibition of DPP-4 activity in plasma by more than 90% at all doses from 10 to 400 mg. The duration of DPP-4 inhibition was dose dependent and to achieve a lasting result the DPP-4 inhibition should be >70 % which corresponds to a dose >10 mg bid. Increases of GLP-1 and GIP concentrations are the expected results of DPP-4 inhibition and studies have confirmed that meal-stimulated as well as between-meal concentrations were raised after 4 week treatment with vildagliptin. Increased concentrations of incretin hormones leads to alfa- and beta-cell stimulation resulting in increased secretion of insulin and reduced glucagon secretion. This was proven in mechanistic studies.
Chronic treatment as well as treatment with a single dose of vildagliptin resulted in reductions of postprandial glucose. In one study, 100 mg and 200 mg vildagliptin was equally effective. There were also evidences for reduced fasting glucose.
Measures of insulin resistance assessed during mechanistic studies of vildagliptin showed tendencies towards increased insulin sensitivity. An improved metabolic state associated with lower glucose levels is predicted to reduce the demand for insulin and thus by definition attenuate insulin resistance. There is few, if any, evidence that vildagliptin has an effect per-se on insulin resistance.

There are unanswered questions concerning secondary pharmacology as the risk of inhibition or activation of other DPP-4 substrates is unclear. These could include vasoactive intestinal peptide (VIP) and neuropeptide Y (potential to alter blood pressure control), bradykinin and substance P (associated angioedema in patients with low DPP-4 activity and taking ACEIs), gastrin and growth hormone release mediators, or immune cytokines. Potential risks associated with these effects are identified in the risk management plan.

No pharmacodynamic studies for metformin were contributed. Metformin decreases glucose levels. It is thought to act by either decreasing gluconeogenesis or decreasing glycogenolysis, as well as enhanced glucose uptake by peripheral tissues such as muscle and fat cells. The combined use with Vildagliptin results in an improved glucose-lowering effect by combining different mechanisms of action.

Clinical efficacy

Overview

Data establishing the clinical efficacy of Eucreas are based on studies with vildagliptin and with vildagliptin using metformin as add-on. Study 2303, testing the combined use of vildagliptin + metformin, is the pivotal study with regard to efficacy. These studies were also part of the data submitted for Galvus, no additional studies had been performed.

Metformin efficacy data
Metformin has been used for more than 40 years and is generally considered as the first line treatment of patients with T2DM. A brief summary of scientific review articles concerning the efficacy of metformin was provided by the applicant. Metformin has been shown to reduce HbA1c levels between -1 and -3%, FPG by 2.78 to 3.9 mmol/L, and some studies have shown positive effects on blood lipid concentrations as well as body weight. The UKPDS showed that overweight patients treated with metformin after failure of diet alone, had a significant reduction of the absolute risk of any diabetes-related complication, myocardial infarction and mortality compared to patients treated with diet alone.

- Dose finding studies

Vildagliptin and metformin was proposed for use in patients with T2DM as fixed combination tablets in 2 strengths: vildagliptin 50mg/ metformin 850mg and 50mg/ metformin 1000mg (both recommended for bid dosing).
In the vildagliptin phase III studies the efficacy of the 100 mg per day regimen was not consistently greater than that of the 50 mg per day regimen. According to results from a meta-analysis, there is an increase in the placebo-subtracted effect of vildagliptin when the dose is increased from 50 mg to 100 mg. This increase is greater in patients with baseline HbA1c of 9.5% (-0.4%) than in those with baseline HbA1C of 8.5% (-0.28%). Although this increase is small, it justifies using 100 mg instead of 50mg daily.

- Vildagliptin monotherapy studies

The monotheraphy studies included patients with characteristic baseline data for T2DM with a rather short duration. Vildagliptin therapy for 24 week resulted in a reduction of HbA1c (~1%) and FPG (~1 mmol/l). Vildagliptin was statistically inferior to metformin 1000 mg bid and may be clinically, although not statistically, inferior to rosiglitazone 8 mg qd (CI for difference between treatments -0.01- 0.39, non-inferiority margin 0.40, ITT population). However, for HbA1c results in the PP population, the upper limit of the CI of the difference between vildagliptin and rosiglitazone exceeded the pre-defined non-inferiority margin of 0.4%. At present there are no data comparing vildagliptin and SU. A comparative study is ongoing. Vildagliptin treatment was largely lipid and weight neutral.

- Vildagliptin+metformin studies

Study 2303 is the pivotal study for this application concerning efficacy. Study 2204 was considered as a supportive study, with a dose of vildagliptin lower than the intended dose of vildagliptin and a duration of only 12 weeks.

Table 1 Studies evaluating the efficacy and safety of the combination vildagliptin/metformin

Study No.	Study objective, population	Randomized patients	Treatment duration	Dosage	Primary efficacy
Placebo-controlled studies					
LAF A2204	Dose selection study in patients inadequately controlled by metformin (HbA1c 7.0% - 9.5%)	132	12 weeks	vilda 50 mg qd+metformin placebo+metformin	change in HbA_{1c}
LAF A2303	Efficacy/safety in T2DM patients inadequately controlled by metformin (HbA_{1c} 7.5% - 11%)	544	24 weeks	vilda 50 mg qd+ metformin vilda 50 mg bid+metformin placebo+metformin	change in HbA_{1c}

METHODS

Study Participants
Patients with T2DM whose glycaemic control was not achieved despite treatment were treated for ≥ 3 months with anti-diabetic drugs and had not achieved adequate glycaemic control.
In the pivotal study 2303, patients were 18-78 years old, had a BMI between 22 and 45 kg/m2 and an HbA1c of 7.5-11%. Patients were on a stable dose of at least 1500 mg metformin daily for a minimum of 4 weeks prior to first visit 1. For a maximum tolerated dose of metformin < 2000 mg daily, either an attempt to reach higher doses in the past was demonstrated or a start with a higher dose at the beginning of the trial was performed. The dose of metformin used at randomization had to be maintained unchanged throughout the trial.

In study 2303, 135 patients were treated with vildagliptin 50 mg bid + metformin 1g bid and 2 patients were treated with vildagliptin 50 mg bid + metformin 850 mg bid.
In study 2204, the vildagliptin 100mg qd arm was prematurely discontinued (due to safety signals in dogs) and thus the results do not include the intended dose of vildagliptin. Furthermore, this study was only of 12 weeks duration.

Endpoints
The primary efficacy parameter was HbA_{1c}. Some of the secondary efficacy parameters included were: FPG, fasting lipids, body weight, some parameters indicative of beta-cell function and insulin resistance, responder rates: (Endpoint HbA_{1c} < 7% / ≤ 6.5%. HbA_{1c} absolute reduction from baseline at endpoint ≥ 1%, / ≥ 0.7%, / ≥ 0.5%).

Statistical methods
The statistical methods used, including the approach to deal with the baseline HbA1c assay issue, were considered to be adequate.
Overall, the design and study population was considered as adequate.

RESULTS

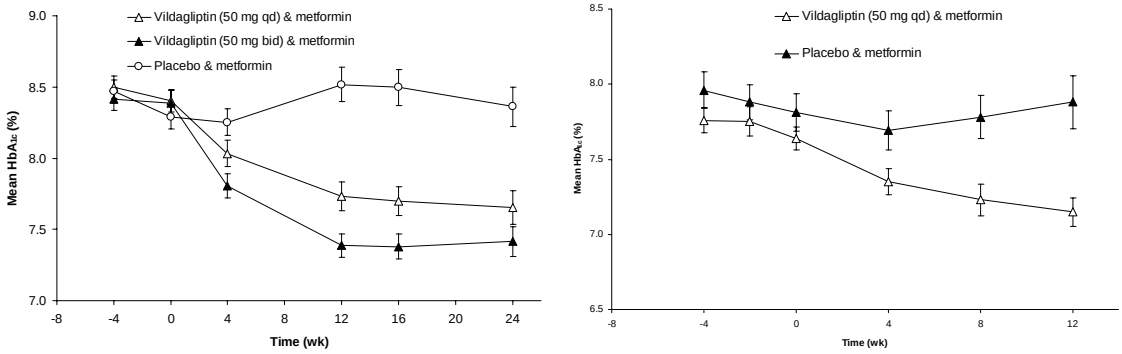
Add-on therapy of metformin to vildagliptin resulted in clinically and statistically significant reductions of HbA1c (0.65% in study 2204 and 0.73 and 1.10 % in study 2303) and FPG (0.98 mmol/L in study 2204 and 0.16 and 1.67 mmol/L in study 2303) compared to placebo.
Body weight slightly decreased in the metformin + placebo group (-1.02 kg). The decrease was less pronounced when vildagliptin 50 mg od was added to metformin (-0.38 kg) while with vildagliptin 50 mg bid there was a slightly increased body weight (+0.21 kg, difference with placebo: p<0.001). Thus, when added to metformin, vildagliptin dose-dependently increased weight up to 1.24 kg on average

compared to metformin alone, but the combined effect of metformin and vildagliptin on weight compared to baseline values was largely weight-neutral.

There was a slight reduction in systolic blood pressure in the vildagliptin groups. Whether this is a result of an improved metabolic state or other mechanisms is not known.

Since vildagliptin is presently not indicated as monotherapy, the additional effect of metformin added to ongoing vildagliptin treatment has not been evaluated.

Fig. 1: Time course of decline in HbA1c from baseline at Week 24/12 (studies 2303 and 2204)



Additional outcomes with the pivotal study 2303

Tab. 2: Change in HbA_{1c} from baseline at Week 24

	N	Baseline HbA_{1c} (%) mean (SE)	Change in HbA_{1c} (%) adj. mean (SE)	Difference to comparator mean (SE)	95% CI	p-value
Primary efficacy ITT population *(ITT population for 1 study)*						
Study 2303 (24 weeks, placebo-controlled add-on combination)						
vilda 50 mg qd + metformin	143	8.38 (0.08)	-0.51 (0.10)	-0.73 (0.14)	(-1.00, -0.47)	<0.001 *
vilda 50 mg bid + metformin	143	8.38 (0.09)	-0.88 (0.10)	-1.10 (0.14)	(-1.37, -0.84)	<0.001 *
placebo + metformin	130	8.30 (0.08)	+0.23 (0.10)			

Tab. 3: Responder analyses for the add-on combination studies

	≥ 0.7% HbA_{1c} reduction			≥ 1.0% HbA_{1c} reduction			HbA_{1c} < 7%		
	Resp. rate %	Diff. to control	p-value	Resp. rate %	Diff. to control	p-value	Resp. rate %	Diff. to control	p-value
Primary efficacy ITT population (*ITT population for 1 study*)									
Study 2303 (24 weeks, placebo-controlled add-on combination)									
vilda 50 qd + metformin	46.2%	26.2%	<0.001	30.8 %	17.7%	<0.001	27.0%	17.6 %	<0.001

vilda 50 bid + metformin	60.1%	40.1%	<0.001	44.1 %	31.0%	<0.00 1	35.5%	26.1 %	<0.001
placebo + metformin	20.0%			13.1 %			9.4%		

No comparisons have been made with other often used add-on alternatives such as metformin +SU, for which efficacy and safety is well documented. Studies are ongoing and the applicant has committed to provide available results. No clinical studies have been performed with the fixed combination product and thus no direct assessment of potential advantages has been performed.

- Clinical studies in special populations

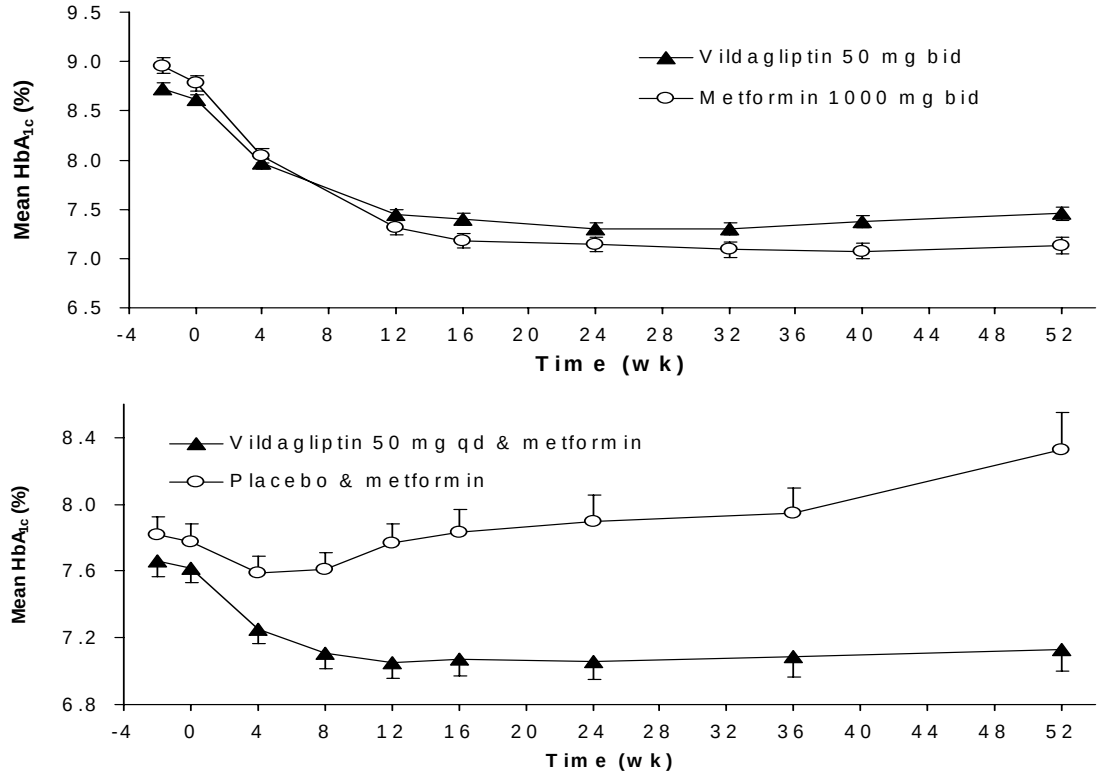
Two-hundred thirty eight patients older than 65 and 41 patients older than 75 years have been treated with the recommended dose of vildagliptin as monotherapy in the primary ITT population. The reduction in HbA1c was somewhat smaller in patients older than 75 years, but the number of patients was limited. Non-obese patients responded better to vildagliptin than obese patients. This difference in efficacy may, at least partly, be explained by increased insulin resistance in obese subjects and may not be of clinical relevance. The efficacy in male patients was larger compared to that in females and the efficacy in black people was smaller compared to that in Caucasians and Hispanics. There is no evident explanation to these differences in efficacy. However, a mean difference of 0.2% between men and women may not be of clinical relevance. Furthermore, no clinically relevant differences in the pharmacokinetics of vildagliptin have been observed between male and female healthy subjects or due to ethnicity.

In combination with metformin, only 7 patients older than 75 years were included in the studies. Given the very small number of patients older than 75 years treated with the combination vildagliptin + metformin, the use of Eucreas is not recommended in this population. Information has been included in the SPC.
Metformin is contraindicated in patients with heart failure, renal and hepatic impairment and thus, Eucreas includes the same contraindications, as listed in the SPC.

Long-term Efficacy data

Concerning long-term efficacy data for vildagliptin, results have been provided from one 52 week study (metformin-controlled, monotherapy, study 2309) and one 40 week extension study following a 12 week core study (add-on therapy to metformin, study 2204), both designed to show efficacy over 1 year (Fig. 2). The proportion of completers after 52 weeks in the monotherapy study was 72% of 780 randomised patients and thus this study provide 1 year efficacy data for vildagliptin as monotherapy in a substantial group of patients. The results achieved after 24 weeks in this study were less pronounced at the week 52 follow-up, but still clinically relevant (mean reduction of HbA1c = 0.96%).

Fig. 2 Mean HbA1c over time in long-term controlled studies (1 year) (monotherapy and add-on to metformin)



During the MAA procedure, data has been provided from a 1 year extension of the 52 week monotherapy study (2309 E1). At 2 years, a 1.0% reduction in HbA_{1c} was observed in the vildagliptin 50 mg bid treatment group compared to a 1.5% reduction in the metformin 1000 mg bid treatment group. However, the durability of the efficacy of vildagliptin will be formally assessed in an ongoing appropriately powered time to failure analysis intended to assess sustainability of glycaemic control.

Long-term efficacy data for vildagliptin as add-on therapy is limited. Only 32 patients treated with vildagliptin plus metformin completed the extension study and these patients were not treated with the recommended dose 50 mg bid. Long-term extension studies are on-going and the Applicant has committed to provide results as FUM.

Clinical safety

- Patient exposure

Metformin has been used in Europe since the 1950s and the safety profile has been well established as patient exposure has been extensive. The safety analysis from Study 2309 includes patients that were exposed to up to 1g metformin bid treatment, over a period of 52 weeks.
Safety data for vildagliptin has been obtained from 3784 patients with T2DM in phase II or III trials of ≥ 12 weeks treatment duration, with 2264 patients receiving vildagliptin as monotherapy and 1520 patients receiving vildagliptin in combination with another medicinal product. The target dose of 100 mg vildagliptin was given to 2682 patients. 274 patients have been exposed to vildagliptin for ≥52 weeks as monotherapy. In total, 441 patients had been treated with vildagliptin and metformin and received at least one dose of study medication, had at least one post-baseline safety assessment and were included in the safety analysis. Overall, the ratios of completers were sufficiently high throughout studies. The number of patients discontinuing due to adverse events did not differ between vildagliptin and placebo groups except for an increased proportion in the vildagliptin+insulin group compared to placebo+insulin group.

- Adverse events

Adverse events in monotherapy studies
Reviews of randomized controlled clinical studies with metformin in the 1990s (including the UKPDS) describe adverse events similar to those in the Glucophage SPC, with up to 50% of the patients suffering from abdominal pain, nausea and diarrhea. The overall incidence of AEs in the 52-week study 2309 was around 75% in the metformin monotherapy group. The most common AEs were gastrointestinal disorders, infections and infestations and nervous system disorders.

The overall incidences of AEs in the three vildagliptin dosing groups in the monotherapy studies were largely comparable to those in the placebo groups. Adverse drug reactions reported at an increased frequency compared to placebo included dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia.
Severe events in the vildagliptin 50 mg bid group were driven by infections and infestations (influenza, bronchitis, nasopharyngitis), occurring in 1.4% of patients versus 0.3% on placebo, and nervous system disorders (0.9% of patients) versus 0.6% on placebo.

Adverse events in combination studies
Adverse drug reactions reported in patients who received Galvus 100 mg in combination with metformin (n=208) were tremor, headache, dizziness, fatigue and nausea.

The overall incidence of AEs in the vildagliptin + metformin and the placebo + metformin groups was similar. Gastrointestinal disorders were less frequent in the vildagliptin + metformin group. There was a higher incidence of headache, dizziness and tremor in the vildagliptin + metformin group compared to placebo.

In the clinical pharmacology studies the adverse events did not differ from those seen in the clinical trials. With high doses of vildagliptin (400 mg and 600 mg), peripheral oedema, pain in extremities, myalgia and paresthesia emerged as dose-dependent AEs.

Angioedema
Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. These cases appear more frequent when vildagliptin is administered in combination with an ACE I. Angioedema will be followed as part of targeted post-marketing activities. Information concerning angioedema is included in section 4.8 of the SPC.

Cardiac adverse events
Since early studies had shown sudden deaths in dogs at high doses of vildagliptin, and a later telemetry study in dogs had shown an effect on cardiac conduction at peak concentrations of high doses of vildagliptin, special focus was placed on the potential for conduction disturbances in human subjects. ECG measurements during exposure to high doses in healthy volunteers showed no effect of vildagliptin on QT/QTc or QRS intervals with doses from 100mg daily up to 400mg. In the clinical studies, there was a higher incidence of first degree AV block in patients treated with vildagliptin as defined by the proportion of patients with PR >200 msec. A majority of the patients with first degree AV block had only moderately increased PR lengths. At this stage the association between vildagliptin and first degree AV block can be neither confirmed nor excluded. Conduction disorder and cardiac events of hypoxic and/or ischemic origin will be evaluated as part of targeted post-marketing activities.

Hypoglycaemia
Metformin has not been shown to produce hypoglycaemia in patients with T2DM or normal subjects (except in special circumstances) and does not cause hyperinsulinemia.

In the monotherapy studies the number of patients with hypoglycaemic events was low in all treatment groups. However, the proportion of patients who reported hypoglycaemic events in the vildagliptin groups was higher with vildagliptin monotherapy (0.4% on vildagliptin 100mg daily) as compared to

placebo (0%), but similar compared to some active controls (0.4% in both the metformin and rosiglitazone groups and 0% in the pioglitazone group).

In the add-on studies with metformin there was no statistically significant increased incidence of hypoglycaemia when vildagliptin was combined with metformin compared to placebo and moreover the proportion of patients who reported hypoglycaemic events in the vildagliptin groups was higher with vildagliptin monotherapy as compared to placebo or metformin.

No severe hypoglycaemic events were reported on vildagliptin.

Skin disorders
Due to the findings of skin lesions in monkeys, the Applicant has performed a review of reported skin disorders in the clinical study program for vildagliptin. Overall, the cases were rather few and of mild severity. The most frequently reported disorders were those of rash and rash-related events. However, rash-related disorders were not similar to the skin lesions observed in the monkey toxicity study. Adverse events such as skin lesions blister and skin ulcer could potentially provide the closest clinical correlation to the types of lesions observed in the monkey study. The incidence rates of selected skin-related events (blister, skin lesion, exfoliation, ulcer and diabetic foot complications) observed for vildagliptin 50mg QD and 100mg daily were similar to the placebo incidence. There did not seem to be a relationship between the vildagliptin dose and skin events.
To alert prescribers to notice potential skin disorders and to provide information concerning the limited experience in patients with skin complications, a warning has been included in SPC section 4.4. Skin events will be part of targeted post-marketing activities

Other potential risks
Potential risks associated with vildagliptin due to hypothetical mechanistic considerations or non clinical findings include drug induced liver injury, infections, muscle events, gastrointestinal haemorrhage and severe hypoglycaemia. These potential risks will be monitored in the PSURs and/ or in the planned post authorisation safety study (angioedema, foot ulcer, hepatic toxicity, serious infections, hypoxic/ischemic cardiac events, peripheral oedema).

- Serious adverse events and deaths

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment. A review of controlled trials involving metformin that lasted at least 1 month, pooled data giving a mean treatment period of 2.1 years. No cases of lactic acidosis were found in 36,000 patient-years of exposure to metformin. However, cases of lactic acidosis continue to be reported in patients taking metformin. Among the first million patients who took metformin in the U.S., there were 47 reports (20 fatal) to the FDA of lactic acidosis. Of these patients, 43 had renal failure or risk factors for lactic acidosis besides metformin (primarily congestive heart failure). A warning is given and precautions recommended in the SPC section 4.4.
SAE were uncommon in all studies and there was no clustering of specific advents associated with vildagliptin treatment. In total, including ongoing studies, there were 50 SAEs with an outcome of death. Of these cases, 26 (6 female and 20 male) patients were exposed to vildagliptin mono- or add-on combination therapy. All 26 of these cases were considered not suspected to be related to study drug. The causes of death included a variety of different conditions and were largely similar in patients treated with vildagliptin and in patients in other treatment groups.

- Safety in special populations

Gender:
In both monotherapy and add-on studies the overall AE rates in females were higher than in males which were not the case in the placebo groups. There is no evident explanation to this difference. The applicant has committed to monitor this as part as routine pharmacovigilance activities.

Elderly:
Elderly patients, in particular those with moderate renal dysfunction, have a notably higher incidence of AEs relative to cardiac disorders and eye disorders although caution is needed in interpretation of these difference due to the low patient numbers in this renal category. Safety data regarding this population will be monitored specifically.

Renal Insufficiency:
The number of subjects with MDRD estimated renal impairment for the monotherapy and add-on therapy datasets was 1870 patients. Of these 198 vildagliptin-treated patients had moderate renal impairment in both datasets combined. In the monotherapy studies there were indications of an increased incidence of overall AE and of gastrointestinal and nervous system disorders in patients with moderate renal insufficiency. Concerning the add-on studies, there were too few patients with moderate renal impairment in each treatment group for an adequate evaluation of safety. However, the overall incidence of AE in patients with moderate renal impairment tended to be higher when vildagliptin was combined with metformin and pioglitazone compared to placebo.
Metformin is contraindicated in patients with impaired renal function (creatinine clearance < 60ml/min). Therefore, this is also a contraindication for the use of Eucreas. Renal function should be checked before starting Eucreas and at least annually during therapy (mentioned in the SPC in section 4.2 as well as 4.4)

Congestive Heart Failure:
Patients with heart failure NYHA III-IV were largely excluded from the clinical studies. Although the data in patients categorized into CHF class NYHA I-II is limited (currently n=62), such patients were included in the clinical trials and their safety profile was not different from that in patients without CHF. The applicant commits to further assess safety in a CHF population in a proposed 12-month post-marketing randomized safety study, through enhanced pharmacovigilance and through the proposed safety cohort study. However since metformin is contra-indicated in patients with heart failure. Therefore Eucreas is also contra-indicated in this population (in section 4.3 of the SPC).

- Laboratory findings

A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials. Therefore, it is recommended in section 4.4 of the SPC that liver function tests be performed prior to the initiation of treatment with Eucreas and periodically thereafter. Eucreas should not be used in patients with severe hepatic impairment.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance System as described by the applicant fulfils the legislative requirements and provides evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for notification of any adverse reaction suspected of occurring either in the community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Transaminase elevations	Routine PVG with targeted monitoring for DILI, see below.	Prescribing information will include precautions and transaminase monitoring. The SmPC will state in [SmPC section 4.4]: A small numerical imbalance of reports of generally asymptomatic elevated transaminases was reported in patients treated with vildagliptin 100 mg daily in controlled clinical trials (see [SmPC section 4.8]). Therefore, as per routine clinical practice, it is recommended that liver function tests be performed prior to the initiation of treatment with vildagliptin and metformin periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be monitored until the abnormalit(ies) return to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of therapy with vildagliptin and metformin is recommended. Vildagliptin and metformin should not be used in patients with hepatic impairment.
Angioedema	Targeted follow up for all cases, aggregate reporting in PSURs, in addition to routine pharmacovigilance. Targeted follow-up and aggregate analysis will include monitoring for concomitant ACEI/ARB use. Angioedema to be a component of post-marketing epidemiologic study.	Angioedema will be included in the [section 4.8 of the SmPC].
Lactic acidosis	Routine PVG and PSUR reporting. Lactic acidosis to be a component of post-marketing epidemiologic study.	Lactic acidosis will be described under [SmPC section 4.4].
Skin lesions with and without concurrent edema and vascular disorder	Targeted monitoring of relevant skin events, vascular and edema events by using appropriately designed questionnaires for follow-up information which will include questions on renal function, monthly and PSUR aggregate reporting with re-assessment at one year, in addition to routine pharmacovigilance. Non-clinical and clinical mechanistic studies Skin lesions to be a component of post-marketing epidemiologic study.	Skin lesions found in monkeys will be described under [SmPC section 4.4], including guidance on observing patients' skin for potentially related manifestations, with a cross reference to non clinical findings in the [SmPC section 5.3]. The patient leaflet will include lay language on observing skin for potentially related manifestations.
Drug-induced liver injury (DILI)	Routine pharmacovigilance plus targeted follow-up of serious clinical trial and spontaneous cases, monthly and PSUR aggregate reporting for one year with re-assessment at that time. Drug-induced liver toxicity to be a	Same as risk minimization activities for transaminases elevations

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	component of post-marketing epidemiologic study.	
Cardiac conduction disturbance	Targeted follow-up of serious reports of AV block with a particular focus on patients with a medical history of AV block and renal impairment, aggregate reporting in PSURs, in addition to routine pharmacovigilance. If available, Novartis will provide data on the incidence of conduction disturbances and other AEs related to cardiac function in high risk patients with hypertension, dyslipidemia and/or cardiovascular disease.	None
Muscle events with and without concurrent statin use	Targeted follow-up of adverse muscle events, such as myalgia and myopathy, as well as for events of greater severity, such as rhabdomyolysis. Since the use of statins may be high in the target population, Novartis would like to differentiate any potential risk with this parameter, as well as differentiating according to degree of renal impairment. Novartis will provide a comprehensive analysis of all subjects/patients exposed to both vildagliptin alone and with statins who have increased CPK levels irrespective of magnitude in the PSUR. The name and dosages of statins administered, duration of statin administration will be indicated. Detailed narratives of these patients will be provided.	None
Hypoglycemia	Routine pharmacovigilance for events of greater severity with targeted follow-up. Queries regarding ACEI/ARB use as part of follow-up.	Listing as an undesirable effect in [SmPC] and described in the prescribing information.
Neurotoxicity	Evidence of neurotoxicity, by evaluating reports pertaining to the MedDRA SOCs Nervous System Disorders and Psychiatric Disorders, will be a topic of interest in the PSURs. This will be re-assessed for appropriateness and any need for greater specificity of terms (eg instead of SOC, using specific PTs) at one year.	None
Serious infections	Targeted follow-up of serious post-marketing reports of infections along with PSUR aggregate review of these reports. Serious infections, as well as those with an outcome of death, will be a component of a population-based post-marketing epidemiologic study.	None
Gender	Novartis will substratify (S)AE reports	None.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
incidence/differences	from clinical trials according to gender in PSURs to look for any increase in the incidence of AEs in women. Post-marketing and spontaneous reports will be examined, as well.	
Patients ≥ 75 years of age	As there is limited information concerning use of vildagliptin and metformin in patients ≥ 75 years of age, safety data regarding this population will be presented separately in clinical trial reports as well as in PSURs and other aggregate reporting, ie monthly for certain events. Data will be substratified for 65-74 and 75+ years.	SmPC will state that there is limited information concerning use of vildagliptin and metformin in patients ≥ 75 years of age and that caution should be exercised when prescribing to this group ([SmPC section 4.2 and 4.4])
Patients with moderate and severe renal impairment	Post-marketing clinical studies in moderate and severe renal impairment. Targeted FU of post-marketing records of skin, cardiac, and hepatic reports for degree of renal impairment.	SmPC will state ([SmPC section 4.2]) that vildagliptin and metformin is contraindicated in patients with creatinine clearance below 60ml/min. In the elderly, the [SmPC] advises regular checks of renal function and that vildagliptin and metformin has not been studied in patients over 75 years of age.
Patients with severe hepatic impairment	With targeted follow-up, there will be questions on hepatic impairment.	SmPC will state that vildagliptin and metformin is contraindicated in patients with hepatic impairment, ([SmPC section 4.2])
Patients with compromised cardiac function	With targeted follow-up, there will be questions on cardiac failure and arrhythmias. The PSUR will monitor cardiac events related to ischemia and hypoxia: eg congestive heart failure; acute coronary syndrome; myocardial infarction; need for invasive procedures, such as CABG, PCI; stroke; cardiovascular deaths, including sudden deaths or deaths of unknown cause. SMQs for Ischemic Heart Disease and Cerebrovascular Disorders, Ischaemic Cerebrovascular Conditions subsearch, will be employed, as well as the MedDRA v.9.1 HLT Vascular Therapeutic Procedures and the Novartis standard PSUR death search, substratified for cardiovascular deaths, sudden deaths, and deaths due to unknown cause. The matched cohort observational study will monitor detailed concomitant treatments, in particular cardio-depressant drugs (including dofetilide).	SmPC will state that there is limited information concerning use of vildagliptin and metformin in patients with heart failure class I and II and that therefore vildagliptin and metformin should be cautiously used in these patients. SmPC will also state that there is no experience of vildagliptin and metformin use in patients with heart failure class III and IV and that therefore use is not recommended in these patients ([SmPC section 4.4])

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

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
At the time of the CHMP opinion, there were a few minor unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. These will be addressed as part of the follow-up measures to be addressed post-authorisation.

Non-clinical pharmacology and toxicology

Essentially no preclicinical studies with the fixed combination Eucreas were conducted, instead the pharmacology and toxicology was mostly studied separately for the vildagliptin and metformin component. Overall, the data presented, as well the analysis of available literature, supported the combined use, and the evidence provided was considered acceptable by the CHMP. Data presented for vildagliptin specifically demonstrated a glucose-lowering effect in animal models of diabetes due to an inhibitory effect on the enzyme DPP-4, thus increasing the levels of incretin hormones which is thought to be the principal mechanism of improvement of glucose homeostasis by vildagliptin.
The general pharmacology studies of vildagliptin showed little safety concerns. Cardiovascular changes at high concentrations in dogs were further investigated in humans and are taken into account within the RMP. The toxicology programme for vildagliptin raised little concern; there were, however, skin-lesions observed in vildagliptin-treated cynomolgus monkeys. The clinical relevance of these findings is unknown, but no equivalent was found in clinical safety studies. Nevertheless, this issue is addressed in the SPC, as well as in follow-up measures.

Efficacy

The efficacy of Eucreas was sufficiently demonstrated. In the absence of clinical efficacy studies conducted with the vildagliptin / metformin fixed-dose combination product, this has been demonstrated by bioequivalence studies together with add-on therapy studies of vildagliptin to metformin, as well as vildagliptin monotherapy studies. Except for the bioequivalence studies, these studies were also part of the data presented by the applicant leading to a positive opinion for vildagliptin (Galvus).

Bioequivalence between the two strengths of the fixed combination and the corresponding free combination was demonstrated for both vildagliptin and metformin AUC and C_{max}, using the normal acceptance criteria 0.80-1.25.

Studies with vildagliptin given alone in T2DM patients showed a reduction of HbA1c (~1%) and FPG (~1 mmol/l) after 24 weeks. The usage as approved is largely based on one pivotal add-on placebo-controlled study and one small supportive study with metformin as a base treatment. The populations studied hereby reflected sufficiently the populations indicated for use.
The pivotal add-on therapy study included patients with inadequate glucose control on monotherapy and achieved clinically relevant reductions of HbA1c by adding a 50 mg bid dose of vildagliptin (0.88 % absolute reduction, 1.10 % reduction compared with metformin alone) after 24 weeks.
Vildagliptin given together with metformin was largely weight neutral. No comparisons have been made with other often used add-on alternatives such as metformin combined with a sulfonylurea.

The recommended dose is 100 mg daily for the vildagliptin component. The recommended dose for metformin is 2000 mg. There are two tablet strengths approved, 50 mg vildagliptin and 850 mg metformin, as well as a second tablet with 50 mg vildagliptin and 1000 mg metformin. This allows the use of 1700 mg metformin with this fixed-dose combination, if this is clinically appropriate.

No study in the paediatric population was performed and therefore the use in this population is not recommended. Experience in patients aged 75 years and older is limited and caution should be exercised with the use in this population.

Safety

Metformin has been used in Europe since the 1950s and has a well-established safety profile due to extensive patient exposure. The vildagliptin safety data was based on 3784 patients with T2DM exposed for ≥ 12 weeks, both as monotherapy or in combination with another antidiabetic product. 274 patients have been exposed to vildagliptin for ≥52 weeks as monotherapy. Data from the combined use was from two studies, where a total number of 441 patients had been treated concomitantly with vildagliptin and metformin.

Common adverse events of a monotherapy with metformin are abdominal pain, nausea and vomiting, diarrhoea, and metallic taste. With vildagliptin monotherapy, the overall incidences of AEs were largely comparable to placebo. Adverse reactions reported at an increased frequency compared to placebo included dizziness, headache, peripheral oedema, constipation, nasopharyngitis, upper respiratory tract infection and arthralgia. In the combined use of vildagliptin with metformin, adverse reactions were reported to include tremor, headache, dizziness, fatigue and nausea.

Eucreas shares some common concerns with vildagliptin (Galvus), in particular reported rare cases of angioedema, a small numerical imbalance of reports of elevated liver enzymes, and a possible association between vildagliptin and first degree AV block (neither confirmed nor excluded at present). In addition, there were preclinical findings with vildagliptin of skin lesions in monkeys (without the detection of a clinical equivalent at present). These issues are identically addressed as for Galvus by text in the SPC and by a commitment of the applicant to perform appropriate follow-up measures. Eucreas shares with metformin the risk of the rare but serious metabolic complication of lactic acidosis. This issue is addressed appropriately with warnings and contraindications (in section 4.3 and 4.4) in the SPC.

The number of hypoglycaemic events was low in patients treated with vildagliptin and metformin. SAE were uncommon in all studies and there was no clustering of specific advents associated with vildagliptin treatment.

There are concerns with regard to the use of vildagliptin in patients with moderate and severe renal impairment. Vildagliptin safety is also not sufficiently assessed in patients with cardiac heart failure. Since both circumstances constitute a contraindication for the use of metformin, Eucreas is contraindicated as well for this patient population.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- **User consultation – To be confirmed and assessed by Raps**

The Applicant performed a user consultation testing on the package leaflet. The design of the test formed the basis of an adequate and competent testing of the PIL in regard to finding, diagnosing and amending possible weaknesses. The present readability test was well designed to meet its main objectives. The results of the user testing described in the user testing report support the changes made to the PIL.

Risk-benefit assessment

Benefits of Eucreas include clinically relevant and significant reductions of HbA1c and FPG compared to placebo. Treatment with Eucreas is also largely weight neutral. However, the therapy

with Eucreas has not been compared to other combination therapies, such as metformin plus sulfonylurea, and long-term efficacy data for Eucreas is limited. Both uncertainties are addressed in ongoing studies, the results of which will be evaluated as follow-up-measures. A presumed benefit of Eucreas is also the expected improvement of compliance by use of two antidiabetic agents in one tablet.
Risks of the use of Eucreas are reported rare cases of angioedema, of elevations of transaminases, and the findings of skin lesions in monkeys. The risk of lactic acidosis due to metformin accumulation is addressed by warnings and contraindications. Eucreas is therefore contraindicated in moderate to severe renal impairment and cardiac heart failure.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Routine pharmacovigilance was adequate to monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of EUCREAS in the treatment of Type II diabetes was favourable and therefore recommended the granting of the marketing authorisation.