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.

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