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. Although being efficient in attenuating hyperglycaemia, all of these treatment alternatives have more or less serious side effects and there is a need for development of efficient drugs without metabolic or other side effects.

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.

The therapeutic indication granted is: Treatment of type 2 diabetes mellitus as dual oral therapy in combination with

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

The recommended dose is 100 mg daily administered either once daily or divided into two doses of 50 mg given in the morning and evening, except for the combined use with a sulphonylurea, where the recommended dose is 50 mg given in the morning.

2 Quality aspects

Introduction

Galvus an immediate release dosage form is presented as tablets containing 50 mg and 100 mg of vildagliptin as active substance. The other ingredients are microcrystalline cellulose, lactose anhydrous, sodium starch glycolate and magnesium stearate.

The film-coated tablets are marketed in aluminium/aluminium (PA/Al/PVC//Al) blisters.

Active Substance

The active substance is 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 for vildagliptin 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 vildagliptin (HPLC), residual solvents (Head-space GC), loss on drying (thermogravimetry), sulphated ash, heavy metals, clarity of solution, colour of solution, assay (by HPLC) and microbiological limit tests.
It was verified that all specifications reflect the relevant quality attributes of the active substance. 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. Certificates of analyses for the active substances were provided and all batch analysis 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 active substance. The 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.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
Galvus tablets were developed five tablet strengths which were used in clinical trials. However, only two tablet strengths (50 mg and 100 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 for that reason different formulation containing different excipients were investigated and optimised.
Having investigated different formulations the applicant selected for commercialisation a direct compression tablet formulation.
Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending and compressing.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps 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 finished product specifications were established according the ICH guidelines and include the following tests: appearance, identification (TLC and HPLC), mean mass, dissolution, water (Karl Fischer), degradation products (HPLC), uniformity of dosage units by mass variation (Ph Eur), or, alternatively, uniformity of dosage units by content uniformity (Ph Eur), assay (HPLC) and 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.
Batch analysis data on three stability batches and three production scale batches (validation batches) confirm satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Three full production scale batches of each strength, as well as a supportive production batch of 100 mg have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was stored under elevated temperature conditions for 3 months and at ICH conditions, and under low temperature conditions for 6 months and 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 studies were performed in accordance with GLP regulations.

Pharmacology

- 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.

- 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.

- 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.

Pharmacokinetics

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 feces. Milk transfer of vildaglitin 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.

Toxicology

- 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

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