Vildagliptin in type 2 diabetes

Summary

Name: Vildagliptin®
Brand: Galvus® (as vildagliptin alone), Eucreas® (as vildagliptin plus metformin)
Company: Novartis Pharmaceuticals UK Ltd
Proposed Indication: Treatment of type 2 diabetes mellitus (T2DM) as dual oral therapy in combination with:
- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin (100mg daily dose administered as 50mg morning and evening)
- 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 (as a 50mg OD dose)
- a thiazolidinedione (‘glitazone’), in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate (50mg BD as for metformin)

Licence status: Marketed March 2008
Cost:
- Vildagliptin 50mg £31.76 for 56 tablets (i.e. £1.13/day for twice daily use)
- Vildagliptin/metformin 50mg/850mg £31.76 for 60 tablets (i.e. £1.06/day for twice daily use)
- Vildagliptin/metformin 50mg/1000mg £31.76 for 60 tablets (i.e. £1.06/day for twice daily use)

- Vildagliptin belongs to a novel class of oral antidiabetic agents, known as dipeptidyl peptidase type 4 (DPP-4) inhibitors. DPP-4 inhibitors work by enhancing the levels of active incretin hormones, which enhance insulin and reduce glucagon secretions, thereby reducing blood glucose levels.
- Management priorities for patients with type 2 diabetes are to control symptoms of diabetes and reduce the risk of diabetes-related events, in particular cardiovascular disease. Effective drug interventions should be directed towards this, rather than simply showing evidence of reductions in markers of blood glucose control such as HbA1c, as the relationship between reductions in HbA1c and cardiovascular risk is not clear.
- Randomised controlled studies have shown that the addition of vildagliptin 50mg OD or 50mg BD to metformin, glimepiride, or pioglitazone produces statistically significant improvements in glycaemic endpoints vs. placebo at 24-weeks. When added to ongoing metformin therapy, vildagliptin was deemed to be non-inferior to pioglitazone in HbA1c reduction at 24 weeks. There are currently no comparative combination therapy data vs. the sulphonylureas.
- The incidence of hypoglycaemia was similar to placebo when vildagliptin was added to metformin or pioglitazone therapy, although when added to ongoing glimepiride, confirmed hypoglycaemia occurred in 0.6% and 1.2% of placebo and vildagliptin 50mg/day recipients, respectively (no statistical analysis available).
- When used in combination with metformin, glimepiride or pioglitazone for 24 weeks, mean body weight changes from baseline for vildagliptin 50mg/day were similar to placebo. However when used in combination with pioglitazone, vildagliptin 50mg BD recipients experienced a statistically significant increase in body weight vs. placebo of around 1kg. When added to ongoing metformin for 24 weeks, mean body weight increases were greater in pioglitazone 30mg/day vs. vildagliptin 50mg BD recipients.
- Vildagliptin is the second DPP-4 inhibitor to be launched in the UK; sitagliptin has been available since April 2007. Currently, only regimens based on metformin have evidence of benefits in patient-oriented outcomes (i.e. living longer or better). Cardiovascular disease is the cause of most of the burden of illness associated with type 2 diabetes and any new therapy should ideally have evidence of benefit in this area before it is routinely used. Such data, in conjunction with robust cost-effectiveness analyses, would inform an assessment of the potential role of vildagliptin in relation to existing therapies used in the overall management of type 2 diabetes.
**Vildagliptin**

*This review updates, and is to be read in conjunction with, ‘Sitagliptin & vildagliptin in type 2 diabetes — On the Horizon, Future Medicines’ [1], produced in December 2006, and available on the NPC website via this link (NHSnet connection required)*

**Introduction**

Diabetes is a chronic progressive disease, which is a major risk factor for coronary heart disease and stroke, and can lead to complications such as kidney failure, blindness and peripheral vascular disease. There are two main types of diabetes, type 1 and type 2. These are very different diseases and are managed in very different ways but type 2 diabetes accounts for approximately 85% of people with diabetes in England [2]. Compared to people of normal weight, the risk of developing type 2 diabetes (T2DM) is almost 13 times greater in obese women, and five times greater in obese men. On average, life expectancy is reduced by between five and seven years in people with T2DM (at age 55 years) [3]. Management priorities for people with type 2 diabetes are to control symptoms of hyperglycaemia and reduce the risk of complications, in particular cardiovascular events. Treatment begins with efforts to improve lifestyle factors, including diet and exercise with consideration given to other interventions to prevent cardiovascular disease. For the management of hyperglycaemia, if the patient fails to respond adequately to a minimum of three months of these measures, the next step is the addition of oral antidiabetic drugs (OADs), usually metformin. Importantly, these should be used to augment the effect of diet and exercise, and not to replace them [4]. Other cardiovascular risk factors such as smoking, hypertension and dyslipidaemia should also be addressed, as these may have a greater impact on morbidity and mortality. Further information on this can be found on the type 2 diabetes floor of NPCi (http://www.npci.org.uk/therapeutics/cardio/diabetes2/room_diabetes2.php).

Vildagliptin belongs to a novel class of OADs, known as dipeptidyl peptidase type 4 (DPP-4) inhibitors. They enhance the levels of active incretin hormones (including glucagon-like peptide 1), which are released steadily by the intestine throughout the day and are increased in response to a meal. Incretin hormones enhance insulin secretion, reduce glucagon secretion, and so reduce blood glucose levels. However, they are rapidly inactivated by the DPP-4 enzyme. DPP-4 inhibitors help to prevent this inactivation [5].

**Efficacy and safety**

Efficacy data relating to the licensed indications of vildagliptin are available from four 24-week randomised, double-blind, phase III studies (three placebo- and one active-controlled). To date, studies have only considered disease-oriented outcomes such as glycosylated haemoglobin (HbA1c) levels rather than the incidence of patient-oriented outcomes such as diabetes-related complications or cardiovascular disease. The placebo-controlled studies randomised T2DM patients with inadequate glycaemic control despite treatment with metformin (≥1500mg/day) [6], pioglitazone (45mg/day) [7], or glimepiride (4mg/day) [8] (Poster) to additional placebo, vildagliptin 50mg once daily, or vildagliptin 50mg twice daily. Vildagliptin recipients had statistically significant reductions in HbA1c vs. placebo, although this would be expected with the addition of any of the existing OADs to T2DM patients failing on monotherapy. Results for major endpoints of these studies are summarised in Table 1.

Vildagliptin has also been compared with pioglitazone in a non-inferiority study of patients already taking metformin. 576 patients who had been uptitrated to at least 1500mg metformin daily, but who still had inadequate glycaemic control (HbA1c ≥7.5%) were randomised to 24-weeks of vildagliptin 50mg BD or pioglitazone 30mg OD, plus on-going metformin [9]. Vildagliptin reached the criterion for non-inferiority (upper-limit 95% CI for between-treatment HbA1c difference ≤0.4% and ≤0.3%). In the published paper, only the results of the per-protocol analysis are available, although a personal communication from Novartis stated that the intention to treat analysis showed similar results. Note that

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**Table 1 - Results for major endpoints of placebo-controlled vildagliptin combination studies**

<table>
<thead>
<tr>
<th></th>
<th>Placebo subtracted adjusted mean decrease in HbA1c [%] (±SE)</th>
<th>Placebo subtracted adjusted mean decrease in fasting plasma glucose [mmol/L] (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vildagliptin 50mg OD</td>
<td>Vildagliptin 50mg OD</td>
</tr>
<tr>
<td>Metformin [6] (n=544) ITT=416</td>
<td>0.70** (0.1)</td>
<td>0.8** (0.3)</td>
</tr>
<tr>
<td>Pioiglitazone [7] (n=463) ITT=398</td>
<td>0.50** (0.1)</td>
<td>0.3* (0.2)</td>
</tr>
<tr>
<td>Glimepiride [8] (n=408)</td>
<td>0.64* (0.1)</td>
<td>0.50† Not available</td>
</tr>
</tbody>
</table>

Results presented for intention to treat (ITT) population.

OD – once a day; BD – twice a day

† Primary endpoint
* P≤0.001
** P≤0.003

† not statistically significant
‡ these dose combinations are not representative of the licensed indications for vildagliptin

Personal communication, Novartis, Sept 2007
non-inferiority studies aim to show that the test drug is no worse than the comparator, which is not quite the same as them being equivalent. Results for major endpoints of this study are summarised in Table 2.

Another phase III study randomised drug-naive type 2 diabetes T2DM patients to vildagliptin 100mg, pioglitazone 30mg, or a combination of vildagliptin and pioglitazone (50/15mg or 100/30mg) once daily [10]. This study of initial combination with a glitazone represents unlicensed use of vildagliptin. Adjusted mean decreases from baseline in HbA1c were 1.1% for vildagliptin, 1.4% for pioglitazone, 1.7% for the 50/15mg combination regimen (P=0.039 vs. pioglitazone alone), and 1.9% for the 100/30mg combination regimen (P=0.001 vs. pioglitazone alone).

Trials have reported that the addition of vildagliptin to existing therapies resulted in an improvement in beta-cell function, as measured by homeostatic model assessment (HOMA) [6, 7, 8]. This in turn led to the suggestion that vildagliptin may have a beneficial effect on beta-cell function. However, it should be noted that HOMA-B is a measure of beta-cell activity, not of beta-cell health or pathology, and results in subjects on insulin secretagogues need to be interpreted with caution [11]. Long-term, robust clinical trials are needed to assess whether vildagliptin can prevent, or even reverse, the decline in beta-cell function seen in T2DM and, more importantly, show that this translates into significant benefits in patient-oriented outcomes. The addition of vildagliptin to metformin, pioglitazone, or gliptin or mepride did not result in clinically meaningful effects on lipid parameters [6,7,8].

It is anticipated that the licensed indications for vildagliptin will expand over time. Fully published data assessing the efficacy of vildagliptin as monotherapy are available from two active-controlled non-inferiority studies [12,13], and two placebo-controlled studies [14,15]. In the active-controlled studies, vildagliptin 50mg BD achieved the criterion for non-inferiority (upper-limit 95% CI for between-treatment HbA1c difference ≤0.4%) vs. rosiglitazone 8mg/day [13], but not vs. metformin 2000mg/day [12]. Both placebo-controlled studies showed statistically significant reductions in HbA1c vs. placebo for vildagliptin 50mg/day and 100mg/day regimens [14,15]. A further 24-week placebo-controlled study (n=296) has evaluated the addition of vildagliptin 50mg BD to T2DM patients with inadequate glycaemic control with insulin monotherapy [16]. Vildagliptin recipients achieved an adjusted mean placebo-subtracted reduction in HbA1c of 0.3% (P=0.01).

When added to ongoing metformin, 18.2% of placebo recipients reported a gastrointestinal adverse event (AE) vs. 9.6% (P<0.05 vs. placebo) and 14.8% of patients receiving vildagliptin 50mg/day, or 50mg BD, respectively [6]. When added to ongoing pioglitazone, peripheral oedema was more common in patients receiving vildagliptin 50mg/day (8.2%), and 50mg BD (7.0%) vs. placebo (2.5%) [7]. However, in the ‘drug-naive study’ peripheral oedema was more common in patients receiving pioglitazone 30mg alone (9.3%) vs. a combination of pioglitazone and vildagliptin (6.1% for the 100/30mg regimen, and 3.5% for the 50/15mg regimen), and vildagliptin alone (5.2%) [9]. Limited data suggest that when added to glimepiride, the overall incidence of AEs was similar for both vildagliptin doses and placebo [8].

The addition of vildagliptin to metformin or pioglitazone did not significantly increase the incidence of hypoglycaemia vs. placebo [6,7], although when added to ongoing glimepiride, confirmed hypoglycaemia occurred in 0.6% and 1.2% of placebo and vildagliptin 50mg/day recipients, respectively (no statistical analysis provided) [8]. No severe hypoglycaemia events were reported in any treatment group [6,7,8].

When added to ongoing metformin, pioglitazone or glimepiride therapy, mean body weight changes were not significantly different between vildagliptin 50mg/day and placebo recipients [6,7,8]. However when added to pioglitazone, vildagliptin 50mg BD recipients experienced a statistically significant increase in body weight vs. placebo of around 1kg [7]. In the active-controlled study, mean body weight increased by 0.3kg and 1.9kg over 24-weeks in vildagliptin 50mg BD, and pioglitazone 30mg/day recipients, respectively (P<0.001; per-protocol analysis) [9]. Information on the use of vildagliptin in the elderly and in patients suffering from renal failure can be found in the Summary of Product Characteristics.

It is important to note that DPP-4 is a relatively non-specific enzyme, which is involved in the metabolism of other plasma peptides in addition to incretin hormones [17]. Whilst there do not seem to have been any clinically significant effects due to reduced metabolism of other plasma proteins noted to date, there are no published safety data beyond one year hence ‘long term’ safety is unknown.

**Place in therapy**

As discussed earlier, management of type 2 diabetes involves the control of glycaemic symptoms and reducing the risk of
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diabetes-related complications, particularly cardiovascular disease. Overall consideration of cardiovascular risk factors is important and interventions such as lifestyle modification, smoking cessation, blood pressure control and use of aspirin and statins have a good evidence-base supporting their use in these patients. Oral hypoglycaemic drugs have an important role in controlling symptoms, particularly for those in whom symptoms persist despite lifestyle interventions but only regimens based on metformin have been shown to reduce the risk of cardiovascular disease. UKPDS also pointed towards an inexorable rise in HbA1c despite tight control of blood glucose [18]. A key question, therefore, is whether any new hypoglycaemic drug can maintain a reduction in HbA1c in the longer term and, crucially, whether use reduces the risk of CV events. Furthermore, and perhaps counter-intuitively, the benefits from metformin may not necessarily be related to its effects on HbA1c [18].

In terms of the use of oral hypoglycaemic agents, existing NICE guidance for T2DM recommends that a sulphonylurea should be used in combination with metformin when glucose control is unsatisfactory [19]. A glitazone may be added to metformin or a sulphonylurea if one of these drugs is contra-indicated or not tolerated [20]. Updated NICE guidance for T2DM is expected to be issued in May 2008 and will take account of any new data that has become available. Sitagliptin and vildagliptin are not covered within this guideline due to late licensing and a limited evidence-base, but are being considered by NICE as part of a rapid update to this guideline, encompassing the newer and more expensive glucose-lowering therapies. The anticipated publication date for this update is February 2009.

Ascertaining the potential role of vildagliptin in the combination treatment of T2DM is difficult. Although their mechanisms of action are different, sulphonylureas and vildagliptin both enhance insulin production, suggesting vildagliptin would compete with sulphonylureas as an ‘add-on’ therapy. However, acquisition costs will be similar to the glitazones, and the only combination study using an active comparator is vs. pioglitazone. Whilst limited, these data indicate that when added to ongoing metformin, vildagliptin and pioglitazone have a similar effect on HbA1c over 24 weeks, but vildagliptin causes less weight gain (although the long-term clinical significance of this is unknown).

Another factor to be taken into consideration is the recent safety concerns regarding the glitazones. They have been found to increase the risk of fractures in women [21], and there is an ongoing debate in the medical literature over their cardiovascular safety [22]. The EMEA has reviewed the cardiovascular safety data for the glitazones and concluded that while the benefits outweigh the risk, they should be only be used in those with existing CV disease after an assessment of the individual risks. MeReC Extra 30 provides a useful summary of the risk/benefit evidence for these agents [22]. There is a particular concern around the potential increased risk of heart failure as highlighted in a recent Drug Safety Bulletin [23]. The SmPC for vildagliptin states that it should be used cautiously in those with mild to moderate heart failure (New York Heart Association (NYHA) class I-II) and is not recommended in those with severe heart failure (NYHA grade III-IV) [24]. This may well impact on future prescribing trends of all drugs for type 2 diabetes, remembering, in particular, the lack of long-term safety data for sitagliptin and vildagliptin.

Vildagliptin is the second DPP-4 inhibitor to be launched in the UK — sitagliptin has been available since April 2007 [25]. Current data suggest that when added to ongoing metformin or pioglitazone therapy, licensed doses of vildagliptin and sitagliptin (100mg/day) both reduce HbA1c [6,7,25]. These studies were performed in different populations and it is unclear whether any differences in the degree of HbA1c reduction are due to different populations or differences between these agents in their ability to lower HbA1c. HbA1c is a surrogate marker and it remains unclear as to whether intensive control of HbA1c using agents other than metformin reduce important clinical macrovascular outcomes such as heart attack or stroke [18]. Vildagliptin appears to be weight-neutral when added to metformin or glimepiride in clinical studies, but may be associated with an increase in weight when combined with pioglitazone — further studies are needed to confirm this.

As for any new therapy in the management of type 2 diabetes, evidence of benefit in patient-oriented outcomes (i.e. living longer or better) are required before vildagliptin should be routinely used. As cardiovascular disease is the cause of most of the burden of illness associated with type 2 diabetes, the effect on this is of particular importance. Such data, in conjunction with robust cost-effectiveness analyses, would inform an assessment of the potential role of vildagliptin in relation to existing combination regimens used in the overall management of type 2 diabetes.
References


21. Short R. Fracture risk is a class effect of glitazones. BMJ 2007;334:551


24. SmPC for Galvus


The information contained herein may be superseded in due course.

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