Emerging Drug List

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Generic (Trade Name): Vildagliptin (Galvus®)

Manufacturer: Novartis

Indication: Type 2 diabetes mellitus

Current Regulatory Status: Vildagliptin has been submitted for approval to Health Canada, and to the US Food and Drug Administration.1

Description: Vildagliptin is one of several incretin enhancer drugs in development.2 The incretin hormones [e.g., glucagon-like peptide (GLP-1)] play a role in maintaining normal blood glucose levels in healthy individuals, but their effects may be diminished in those with diabetes. GLP-1 stimulates the secretion of insulin from the pancreas as blood glucose levels rise after a meal. It has several other actions, such as delaying gastric emptying and suppressing glucagon secretion, that help control blood glucose levels. Vildagliptin increases the levels of GLP-1 by inhibiting dipeptidyl peptidase-4, the enzyme that inactivates GLP-1.2 In clinical trials, vildagliptin was administered orally, as monotherapy, and in combination with other hypoglycemic agents.

Current Treatment: Therapies for type 2 diabetes include diet, exercise, and pharmacotherapy. Several oral hypoglycemic agents are available in Canada. These include sulfonylureas (e.g., glyburide, gliclazide, glimepiride) and other insulin secretagogues (e.g., nateglinide, repaglinide), biguanides (e.g., metformin), alpha-glucosidase inhibitors (e.g., acarbose), and thiazolidinediones (e.g., pioglitazone, rosiglitazone). These oral agents may be prescribed alone, or as combination therapy. Insulin may also be required by some patients with type 2 diabetes who cannot maintain satisfactory blood glucose levels.3

Cost: No cost information is available for vildagliptin.

Evidence: Vildagliptin has been studied in several phase II and III trials. The phase III trials are ongoing, or have been published as abstracts.4-7

In two double-blind phase II trials, treatment-naïve patients with type 2 diabetes were randomized to receive 12 weeks of vildagliptin or placebo.8,9 In the study by Ristic et al.,8 279 patients were treated with vildagliptin (25 mg twice daily, 25 mg, 50 mg, or 100 mg once daily), or placebo. At the end of the study period, all groups had decreases in the glycosylated hemoglobin (A1C) levels compared to baseline. The reductions in the A1C levels for the vildagliptin 50 mg (–0.56%) and the 100 mg groups (–0.53%) were significantly greater than that for the placebo group (p<0.05).8

In the study by Pratley et al.,9 100 patients were randomized to receive vildagliptin 25 mg twice daily, or placebo. After 12 weeks of therapy, the adjusted mean change in the A1C levels was significantly different for the vildagliptin group than for the placebo group (between-group difference −0.6%±0.2% p=0.0012). The fasting plasma glucose level was significantly lower in the vildagliptin group.9
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In the phase II study by Ahren et al.,10 107 patients stabilized on metformin (1,500 to 3,000 mg per day) were randomized to receive vildagliptin 50 mg daily or placebo. After the 12-week core study, 42 patients in the vildagliptin group and 29 in the placebo group continued blinded treatment for another 40 weeks. At 12 weeks, the A1C level was significantly lower in the vildagliptin group than in the placebo group (between-group difference −0.7%±0.1%, p<0.0001). This significant difference favouring vildagliptin was maintained in the subset of patients who completed up to 52 weeks of therapy.10

At the 2006 meeting of the American Diabetes Association, the results of several vildagliptin trials were presented. Four phase III randomized double-blind trials enrolled 256 to 780 patients with type 2 diabetes.4-7 The dose of vildagliptin evaluated was 50 mg daily in one trial,6 and 50 mg twice daily in four trials.4-7 Vildagliptin or placebo was added to metformin treatment6 in one study, and to insulin in a second study.7 Another study compared vildagliptin to rosiglitazone,7 while yet another compared it to metformin.5 Three trials5-7 were 24 weeks, and one6 was 52 weeks in duration. The change in A1C levels was reported in all abstracts.

In the 52-week trial in drug-naïve patients, the vildagliptin and metformin (1,000 mg twice daily) groups showed a reduction in A1C (adjusted mean change from baseline: vildagliptin −1.0%±0.1%, metformin −1.4%±0.1%). The between-group difference did not establish the non-inferiority of vildagliptin versus metformin.4 In a similar population treated with vildagliptin or rosiglitazone (8 mg daily) for 24 weeks, the adjusted mean change in A1C from baseline was −1.1%±0.1% for vildagliptin (rosiglitazone data were not reported). The abstract concluded that vildagliptin’s non-inferiority to rosiglitazone was established.5

In the trial comparing 50 mg or 100 mg per day of vildagliptin plus metformin to placebo plus metformin, both vildagliptin groups reported a statistically significant reduction in A1C compared to placebo plus metformin. The between-group difference in the A1C adjusted mean change was −0.7%±0.1% for vildagliptin 50 mg plus metformin, and −1.1%±0.1% for vildagliptin 100 mg plus metformin (p<0.001), versus placebo plus metformin.6

In patients who are inadequately controlled on insulin, adding vildagliptin significantly reduced the A1C relative to placebo (adjusted mean change from baseline: vildagliptin plus insulin −0.5%±0.1%; placebo plus insulin −0.2%±0.1%, p=0.022).7

In the phase II trials comparing vildagliptin to placebo,6-9 the numbers of adverse events (AE), serious adverse events (SAE), or discontinuations due to AE were similar between groups. There were three episodes of symptomatic hypoglycemia in the vildagliptin-treated patients. The AE reported in >5% of patients were headache, nasopharyngitis, hypoglycemia, dizziness, peripheral edema, increased sweating, hypertension, gastrointestinal symptoms, and cough. Similar rates of these AE were reported in the placebo groups.

In the study by Ahren et al.,10 three patients on vildagliptin plus metformin experienced worsening of hypertension and required treatment, and one patient reported peripheral

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**Adverse Effects:**

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edema. Two patients in the vildagliptin group experienced one episode of symptomatic hypoglycemia. The overall rates of AE and SAE were similar between groups.

A similar incidence of AE was reported for vildagliptin and comparators in all the phase III trials, but the data were limited in the study abstracts. In three trials, the number of hypoglycemic events was similar between the groups taking vildagliptin or comparators. In one study, the vildagliptin plus insulin group reported fewer hypoglycemic events than the placebo plus insulin group (statistical significance not reported).

Five studies reported that body weight remained stable in vildagliptin-treated patients. Compared to placebo, there was no significant change in body weight after 12 weeks of vildagliptin therapy.

Commentary:

Over two million Canadians have diabetes, and this number is expected to increase to three million by 2010. Among these individuals, 90% have type 2 diabetes. Health care expenditures to treat diabetes are increasing as the prevalence of the disease rises. In Saskatchewan in 2001, total health care expenditures (excluding prescription drugs) for people with diabetes was C$154 million, up from C$140 million in 1991. In 2001, the average health care expenditure per person with diabetes was C$3,372, which was almost three times higher than that for the general population.

Incretin enhancers, such as vildagliptin, sitagliptin, and saxagliptin, are a new therapeutic class of oral agents for the treatment of diabetes. To determine vildagliptin’s place in therapy, additional information on its efficacy, safety, and cost is required. More research is underway, and as of September 28, 2006, ClinicalTrials.gov showed 11 ongoing trials with vildagliptin. Currently, the evidence with vildagliptin is limited to surrogate markers of effectiveness (e.g., A1C). Longer-term clinical research is needed to establish the clinical benefits of vildagliptin (i.e., reduction of diabetes complications, and long-term tolerance). As a result, it may not be possible to establish the clinical and cost effectiveness of vildagliptin versus other hypoglycemic agents for some time.

References:


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