

sitagliptin, 100mg film-coated tablet (Januvia®)

No. (607/10)

Merck Sharp & Dohme Ltd

04 June 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sitagliptin (Januvia®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: as monotherapy, to improve glycaemic control in patients with type 2 diabetes mellitus who are inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

SMC restriction: to patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.

Sitagliptin met the pre-defined efficacy criterion for non-inferiority versus metformin in a study of treatment naïve patients. It appears to have minimal effect on body weight.

The health economic case was demonstrated only for a sub-population of patients within the licensed indication.

The licensed indication for sitagliptin has also recently been extended to include use in triple combination therapy with metformin plus thiazolidinediones and use as add-on therapy to insulin. The manufacturer's submission related only to the use of sitagliptin as monotherapy. Therefore SMC cannot recommend the use of sitagliptin in combination with metformin plus thiazolidinediones or as add-on therapy to insulin.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

To improve glycaemic control in patients with type 2 diabetes mellitus as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

Sitagliptin is also indicated to improve glycaemic control in patients with type 2 diabetes mellitus

- as dual oral therapy in combination with

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a PPAR γ agonist (i.e. a thiazolidinedione) when use of a PPAR γ agonist is appropriate and when diet and exercise plus the PPAR γ agonist alone do not provide adequate glycaemic control.

- as triple oral therapy in combination with

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
- a PPAR γ agonist and metformin when use of a PPAR γ agonist is appropriate and when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

Sitagliptin is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control.

Dosing information

100mg once daily, with or without food.

Product availability date

29 July 2009

Summary of evidence on comparative efficacy

Sitagliptin inhibits the enzyme dipeptidyl peptidase-IV (DPP-4), preventing the degradation of incretin hormones, which are released from gut cells in response to a meal. These hormones stimulate insulin release and attenuate glucagon secretion in response to raised blood glucose levels.

This submission relates to a recent licence extension for sitagliptin to allow its use as monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance. The submitting company has requested that the Scottish Medicines Consortium considers its use in a further restricted population, namely in those for whom not only metformin but also a sulphonylurea is inappropriate.

A 24-week phase III, double-blind, randomised study recruited patients with type 2 diabetes mellitus aged 18 to 78 years. Patients were treatment naïve (defined as not having taken an antihyperglycaemic agent for at least 16 weeks prior to study entry) with a glycated haemoglobin (HbA1c) level of 6.5 to 9.0%.

After a 2-week placebo run-in period, patients were randomised equally to either sitagliptin 100mg once daily or metformin 1,000mg twice daily, with the metformin dose being up-titrated over a 5-week period. Patients discontinued due to lack of efficacy according to progressively stricter glycaemic criteria, based on fasting plasma glucose (FPG) levels.

The primary analysis assessed whether sitagliptin was non-inferior to metformin, based on HbA1c change from baseline at week 24. Comparison was made using the least squares (LS) means of the two treatment groups as estimated via analysis of covariance (ANCOVA) in the per protocol (PP) population, defined as those patients who completed the study and had baseline and week 24 on-treatment data with no major protocol violations. Non-inferiority was demonstrated if the upper boundary of the 95% confidence interval (CI) for the between-group difference was less than 0.4%. Other end-points included proportions of patients with HbA1c <6.5% and <7% and fasting plasma glucose levels.

Patients with mild to moderate hyperglycaemia and a mean HbA1c of 7.2% (n=1050) were randomised. Approximately 84% of patients had an HbA1c <8%, with approximately 43% with an HbA1c <7%. In the PP population (n=894), the LS mean HbA1c change from baseline at week 24 was -0.43% (95%CI: -0.48 to -0.38) in the sitagliptin group (n=455) and -0.57% (95%CI: -0.62 to -0.51) in the metformin group (n=439). The estimated difference in LS means for sitagliptin versus metformin was 0.14% (95% CI: 0.06 to 0.21). The upper limit of the two-sided 95% CI was less than the pre-specified non-inferiority margin of 0.40%, thus non-inferiority of sitagliptin to metformin was demonstrated. This primary PP analysis was supported by an analysis based on the full analysis set population. The LS mean change in HbA1c from baseline at week 24 was -0.38% (95% CI: - 0.43 to -0.32) in the sitagliptin group (n = 512) and -0.55% (95%CI: -0.61 to -0.50) in the metformin group (n = 498). The estimated difference in LS means for sitagliptin versus metformin in this supportive analysis was 0.18% (95% CI: 0.10 to 0.25).

The proportion of patients with an HbA1c <7% at week 24 was greater with metformin (76%) compared with sitagliptin (69%) [between-treatment difference in proportions: -7.1% (95% CI: -12.9 to -1.2)], whereas the proportion of patients with an HbA1c <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups [between-treatment difference in proportions -5.6% (95% CI: -11.8 to 0.8)]. LS mean change from baseline in FPG (where mean baseline was 7.9mmol/L) was greater with metformin (-1.1mmol/L) compared with sitagliptin (-0.6mmol/L). The profiles of mean change from baseline in FPG over time showed that both treatment groups exhibited similar trends, beginning with a decrease in the first 6 weeks followed by stable levels for the remainder of the study.

Summary of evidence on comparative safety

In general, both sitagliptin and metformin were well tolerated, with no unexpected adverse events observed. The incidence of adverse events was 41% with metformin and 38% with sitagliptin. The incidence of adverse events leading to discontinuation was higher in the metformin group, primarily due to a higher rate of gastrointestinal adverse events (21% versus 12%).

Hypoglycaemia was reported by 3.3% of patients in the metformin group and 1.7% in the sitagliptin group. All drug-related events that led to discontinuation in the sitagliptin group were due to hypoglycaemia. There was a mean decrease in body weight observed in both sitagliptin and metformin groups (-0.6 kg versus -1.9 kg).

There was a small increase in the overall incidence of cardiac adverse events reported with sitagliptin although the incidence of serious cardiac adverse events was lower with sitagliptin group than with metformin. These adverse events are being monitored in an on-going cardiovascular outcome study.

Summary of clinical effectiveness issues

The pivotal monotherapy study submitted to the European Medicines Agency (EMA) demonstrated non-inferiority of sitagliptin to metformin. Study limitations included a large margin for non-inferiority which the Committee of Medical Products for Humans (CHMP) considered excessive, a low mean baseline HbA1c and a short study duration. The CHMP concluded that although the pre-defined criterion for non-inferiority was met, non-inferiority was not unequivocally demonstrated. The primary and secondary efficacy results and the drop out rates due to lack of efficacy (10/528 in the sitagliptin group versus 1/522 in the metformin group) suggested that sitagliptin is less effective than metformin. In addition, the differences between sitagliptin and metformin appeared to widen over time and 12-month comparative data would have been preferable to demonstrate maintenance of effect. Hence the monotherapy indication for sitagliptin was approved only as second-line therapy to metformin.

The submitting company has requested that SMC consider the use of this product in a sub-population of the licensed indication, namely patients for whom the use of both metformin and a sulphonylurea is inappropriate (e.g. because of experience of hypoglycaemia following a trial with a sulphonylurea, or significant concern of hypoglycaemia or weight gain). No reference to this potential patient population appears in national guidance on diabetes and its size is unknown. No efficacy or safety evidence has been submitted for this specific patient population.

Head-to-head clinical study data are not available against relevant comparators in clinical practice for the monotherapy indication. In patients inadequately controlled on metformin monotherapy, sitagliptin has demonstrated efficacy comparable with rosiglitazone and with glipizide, when these are added to metformin. There is no clinical evidence to suggest that these results can be extrapolated to monotherapy. In the absence of direct comparative data, an indirect comparison was made in the economic case and, due to changing patterns of prescribing of thiazolidinediones in Scotland, pioglitazone was used.

Published studies have reported greater reductions in HbA1c with rosiglitazone or pioglitazone than with sitagliptin. In order to address potential confounding factors, a recently published meta-analysis of 23 studies, used as the basis of the indirect comparison, investigated the relationship between baseline HbA1c and perceived efficacy of treatment. When the term accounting for baseline HbA1c level was included in the model used, all agents were found to be similarly effective. Most of these studies used combination therapy, not monotherapy.

A Cochrane review of DPP-4 inhibitors for type 2 diabetes mellitus was published in 2008 and discussed sitagliptin and vildagliptin. No data had been published on mortality, diabetic complications, costs of treatment and health-related quality of life. Sitagliptin therapy in comparison with placebo resulted in an HbA1c reduction of approximately 0.7%. Comparisons with established blood-glucose lowering drugs did not reveal advantages of DPP-4 inhibitor treatment. Weight gain was not observed and no severe hypoglycaemia was reported with sitagliptin therapy, however all-cause infections increased significantly after sitagliptin treatment. The authors concluded that long-term data on cardiovascular outcomes and safety and all-cause mortality are needed.

No new safety issues were identified in the pivotal study although the long-term safety of sitagliptin has yet to be established. Acute pancreatitis has been reported in patients taking sitagliptin and the US Food and Drugs Agency is consequently revising its prescribing information to advise monitoring for this condition.

Summary of comparative health economic evidence

The manufacturer presented two analyses of sitagliptin as a monotherapy:

- A simple cost-minimisation analysis between sitagliptin and pioglitazone 30mg;
- A more complicated lifetime individual patient cost utility model developed by the manufacturer [Januvia Diabetes Economic model: JADE] again using pioglitazone 30mg as the comparator.

The patient population of interest was for patients in whom both metformin and sulphonylureas were inappropriate due to contraindications or intolerance.

Cost-minimisation was justified by the manufacturer on the basis of a mixed treatment comparison of sitagliptin, pioglitazone and rosiglitazone that found no difference between treatments in terms of glycaemic control once baseline HbA1c had been controlled for. This mixed treatment comparison encompassed a range of papers including monotherapy, dual therapy and triple therapy. The manufacturer subsequently provided a meta-analysis that was confined to monotherapy studies to address SMC's concerns about the heterogeneous nature of this clinical evidence.

The JADE modelling assumed that sitagliptin was clinically equivalent to pioglitazone in terms of its effect upon HbA1c. The main anticipated benefits from sitagliptin arose from:

- pioglitazone having a relative risk of CHF of 1.41 compared to sitagliptin;
- pioglitazone leading to a 3kg weight gain compared to a 0.65kg weight loss for sitagliptin;
- some additional differentiation between treatments in terms of systolic blood pressure and lipids profiles.

The cost-minimisation found sitagliptin to be less expensive than pioglitazone 30mg by £34 per patient per annum.

The cost-utility modelling found that sitagliptin was both more effective, with a QALY gain of 0.025, and less costly, with a cost saving of £274, so was estimated as dominating pioglitazone 30mg.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a Management of Diabetes guideline (number 116), in March 2010. It recommends that metformin be considered as the first-line treatment option for overweight patients with type 2 diabetes mellitus who have inadequate glycaemic control on diet alone. Sulphonylureas may also be considered as first-line agents in patients who are not overweight and who are intolerant of, or have contraindications to, metformin. DPP-4 inhibitors are included as an option for add-

on therapy, second or third-line. The guideline predates the use of DPP-4 inhibitors as monotherapy. In terms of targets for glycaemic control, SIGN recommends that an HbA1c target of 7.0% among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease and that a target of 6.5% may be appropriate at diagnosis.

The National Institute for Health and Clinical Excellence (NICE) published Clinical Guideline 87, the management of type 2 diabetes, in May 2009. The guideline predates the use of DPP-4 inhibitors as monotherapy but recommends that these agents can be considered as second or third-line treatment options.

Additional information: comparators

In type 2 diabetes mellitus patients for whom the use of metformin is inappropriate, monotherapy options are sulphonylureas, repaglinide, and peroxisome proliferator-activated receptor- γ agonists. The SMC has previously restricted rosiglitazone and pioglitazone monotherapy to patients in whom consideration is otherwise being given to commencing insulin therapy and who have already experienced severe hypoglycaemia or in whom metformin and sulphonylureas are contra-indicated or not tolerated.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Sitagliptin	100mg daily orally	432
Sulphonylureas		
Glipizide	2.5 to 20mg daily orally*	8 to 66
Tolbutamide	500 to 1500mg daily orally	20 to 60
Gliclazide	40 to 320mg daily orally*	7 to 59
Glimepiride	1 to 4mg daily	20 to 49
Peroxisome proliferator-activated receptor-γ agonists		
Pioglitazone	15 to 45mg daily orally	336 to 514
Rosiglitazone	4 to 8mg daily orally	260 to 390
Meglitinides		
Repaglinide	0.5mg twice daily to 4mg four times daily orally	95 to 381

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 17.02.10. * Higher total daily doses should be divided..

Additional information: budget impact

The manufacturer estimated a gross drug cost of £67k in year 1, rising to £207k by year 5. Given the displacement of pioglitazone 30mg this resulted in a net drug cost saving of £5k in year 1, rising to £16k by year 5.

The estimates were based on the assumption that there are around 1,500 patients with diabetes currently receiving thiazolidinedione monotherapy. It was assumed that an initial 10% would receive sitagliptin in year 1, rising to 30% by year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 19 April 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC

The undernoted reference was supplied with the submission. The reference shaded grey is additional to that supplied with the submission.

Ascher P, Katzeff HL, Guo H et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes Obes Metab* 2010; 12:252-61.

European Medicines Agency. European Public Assessment Report: Januvia®. July 2009. EMEA H-C-722/II/0008
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