Scottish Medicines Consortium

sitagliptin 100mg tablets (Januvia®) No. (408/07)
Merck, Sharpe & Dohme Limited

7 September 2007

The Scottish Medicines Consortium 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 for treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin, do not provide adequate glycaemic control. It should be restricted to use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones.

Efficacy, as assessed by measurement of HbA1c, is similar to sulphonylurea and thiazolidinedione drugs added at this stage in therapy. It appears to have minimal effects on body weight.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin, do not provide adequate glycaemic control.

Dosing information

100mg once daily. The dosage of metformin should be maintained and sitagliptin administered concomitantly.

Product availability date

20 April 2007

Summary of evidence on comparative efficacy

Sitagliptin inhibits dipeptidyl peptidase 4 (DPP-IV) and thus prevents 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.

Two active comparator studies recruited patients aged 18 to 78 years with type 2 diabetes who had inadequate glycaemic control while receiving a stable dose of metformin ≥1500mg/day. Sitagliptin 100mg once daily or comparators were given on a background of metformin ≥1500mg/day.

The first was a non-inferiority study in which either sitagliptin or glipizide (titrated to ≤20mg/day), was added to metformin, and the primary efficacy outcome was the change in HbA_{1c} from baseline to 52 weeks. In this study inadequate glycaemic control was defined as HbA_{1c} ≥6.5% to ≤10%, either at screening or following a metformin titration and dose stabilisation period. The primary analysis was in the per-protocol (PP) population, restricted to those who completed 52 weeks of treatment with no reasons for exclusion, such as incomplete data points or protocol violations. This comprised 793 patients: 382/588 (65%) of patients randomised to sitagliptin and 411/584 (70%) of patients randomised to glipizide. An all-patients-treated (APT) analysis was also carried out for all randomised patients who had received at least one dose of study medication and had both a baseline and at least one post-baseline measurement. This included 576/588 (98%) of patients randomised to sitagliptin and 559/584 (96%) of patients randomised to glipizide.

In both sitagliptin and glipizide groups there was a decrease in HbA_{1c} over the first 24 to 30 weeks, followed by an increase so that, in the per-protocol analysis at 52 weeks, both the sitagliptin and the glipizide groups had achieved the same change in least squares mean HbA_{1c} (-0.67%) from a baseline of 7.5%. This represented a between-group least square mean difference of –0.01% (95% confidence intervals [CI]: -0.09, 0.08). The upper limit of the CI for the between-group difference was below the pre-specified non-inferiority margin of 0.3%. In the APT population the between-group difference was 0.04% (95% CI: –0.04, 0.13).

A similar number of patients achieved HbA_{1c} <7% with sitagliptin and glipizide (63% and 59% respectively) and most other glycaemic outcomes and lipid parameters were not significantly different between groups.

Least squares mean HbA_{1c} (%), changes from baseline to end-point and treatment differences in two active comparator randomised controlled trials.

	n	Baseline	End-point	Difference from baseline (95% CI)	Difference sitagliptin - comparator (95% CI)
Sitagliptin vs glipizide Per protocol population			52 weeks		
Sitagliptin 100mg od	382	7.5	6.8	-0.67 (-0.75, -0.59)	
Glipizide ≤20mg od	411	7.5	6.9	-0.67 (-0.75, -0.59)	-0.01 (-0.09. 0.08)

od = once daily; CI = confidence intervals

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the first study, 30% of randomised patients who had received at least one dose of study drug in the glipizide/ metformin group experienced adverse events which were considered to be related to trial drug, compared with 14% in the sitagliptin/ metformin group. This was mainly related to a higher incidence of hypoglycaemia in the glipizide group when compared with the sitagliptin group (32% versus 4.9%). Two events considered related to the study drug were serious, both in the glipizide group. The incidence of gastro-intestinal events was not significantly different between treatments. The addition of sitagliptin to metformin reduced mean body weight by 1.5kg compared with an increase of 1.1kg with the addition of glipizide ($p<0.001$).

Summary of clinical effectiveness issues

In the comparative trial versus glipizide, in which the primary analysis was performed on the PP population, more patients in the sitagliptin group discontinued treatment, the excess being due to discontinuation for lack of efficacy. Patients in the sitagliptin group tended to discontinue earlier in the study than patients in the glipizide group.

These, and other differences in the character of patients who discontinued, are a potential source of bias. For example, in the PP population, patients excluded because of lack of efficacy are likely to have relatively high values of HbA_{1c} and, in the APT analysis, patients who discontinue early may carry forward different values from those who discontinue later. However, the potential influence of these factors on trial outcomes and comparisons between groups is not clear, and both the published paper and the European Medicines Agency's European Public Assessment Report (EPAR) comment on the similarity of results for the primary end point in PP and APT analyses.

Long-term studies are needed to determine the effects of sitagliptin on disease-related morbidity and mortality.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing sitagliptin to either rosiglitazone or sulphonylurea, where each drug was added to existing treatment with metformin. A lifetime model was used and patients could progress to other treatments (such as insulin) depending on their response to therapy. The model structure allowed for risk factors (e.g. HbA1c and weight) and adverse events to influence the outcomes in the model and there was also the inclusion of diabetes-related complications. Changes in HbA1c occurred in two stages; an initial drop followed by a rise which occurred at a fixed rate over time. When HbA1c levels reached a pre-defined threshold (8%) the treatment was changed. Long term outcomes in the model were estimated using UKPDS risk factor equations. Increased rates of congestive heart failure were included for rosiglitazone but no account was taken of the recently published issue of potentially increased myocardial infarction and cardiovascular death. The resulting incremental costs per QALY were £18437 for the comparison with sulphonylurea or £619 for the comparison with rosiglitazone. The high cost per QALY in the comparison with sulphonylurea is a function of comparable efficacy but higher drug acquisition costs for sitagliptin.

A number of points should be noted in terms of the analysis, particularly in relation to the cost effectiveness compared to sulphonylurea. The first was an adjustment to take account of the initial drop in HbA1c at 24 weeks, which was estimated from the 52 week trial results of the study comparing sitagliptin to sulphonylurea. In sensitivity analysis, changing this parameter by 10% increased the ICER to £21,828 but it is likely that the assumptions made on this aspect are still biased in favour of sitagliptin.

Secondly, the results of both pieces of analysis include a benefit in terms of weight gain in favour of sitagliptin which was then assumed to result in lower costs and higher utility. The results were sensitive to changes in this assumption. For example, in the comparison with sulphonylureas, if the utility changes for weight gain were reduced by 50% then the ICER rose to £23344. In addition, the model assumed that utility value decrements for multiple co-morbidities were additive, since this is the assumption contained in the source study (UKPDS). However, assuming additive utility decrements for multiple comorbidities can result in relatively low utility values, which can bias the results in favour of the intervention which is more effective at preventing co-morbidities. Given these limitations, there is upward uncertainty in the cost-effectiveness of sitagliptin compared to sulphonylurea leading to the conclusion that the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC. However, the economic case compared to rosiglitazone was demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Diabetes UK Scotland

Additional information: previous SMC advice

7 April 2006 (Issued August 2006) following an abbreviated submission
Pioglitazone 15mg/metformin 850mg hydrochloride (Competact®) is accepted for restricted use in NHSScotland for the treatment of type 2 diabetes mellitus. It should be used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone. It is restricted to patients who cannot be treated with

a sulphonylurea in combination with metformin. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient, though less flexible, dosing regimen.

9 February 2007 following a full submission
Pioglitazone (Actos®), as triple therapy in combination with metformin and a sulphonylurea, is accepted for restricted use within NHS Scotland for the treatment of patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy and where patients are unable or unwilling to take insulin. It should be initiated and monitored only by physicians experienced in the treatment of diabetes mellitus who will be able to identify and manage patients who might benefit.

8 February 2004 following an abbreviated submission.
Rosiglitazone, metformin (Avandamet®) is accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus. It is used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone and cannot be treated with a sulphonylurea in combination with metformin. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient dosing regimen, though less flexible.

6 May 2005 following an abbreviated submission
Rosiglitazone (Avandia®) is accepted for restricted use in NHS Scotland as triple oral therapy in combination with metformin and a sulphonylurea in patients (particularly overweight patients) who are unable to achieve sufficient glycaemic control despite dual oral therapy and where patients are unable or unwilling to take insulin. It should be initiated and monitored only by physicians experienced in the treatment of diabetes mellitus who will be able to identify and manage patients who might benefit.

9 June 2006 following an abbreviated submission
Rosiglitazone / metformin tablet (Avandamet) is accepted for restricted use within NHS Scotland in combination with a sulphonylurea as triple oral therapy in patients (particularly in overweight patients) who are unable to achieve sufficient glycaemic control despite dual oral therapy and where patients are unable or unwilling to take insulin. Triple therapy should be initiated and monitored only by physicians experienced in the treatment of diabetes mellitus who will be able to identify and manage patients who might benefit. The combination formulations are not associated with increased costs compared to equivalent combinations of single drug formulations.

8 June 2007 following a full submission
Exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. It has shown non-inferiority to two insulin regimens with which it has been compared and has a beneficial effect on weight. It is restricted to use as an alternative to insulin in patients who have failed treatment on metformin and/or sulphonylureas and in whom insulin would be the next treatment option.

Additional information: comparators

Acarbose can be used in diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs. Nateglinide and repaglinide can be used in combination with metformin, and repaglinide as monotherapy, in type 2 diabetes mellitus when metformin alone is inadequate.

Pioglitazone and rosiglitazone can be used in type 2 diabetes alone, or in combination with metformin and/or a sulphonylurea (dual or triple therapy).

Exenatide, which mimics the effects of incretin hormones, can be used for the treatment of type 2 diabetes mellitus, in combination with metformin and/or sulphonylureas, in patients who have not achieved adequate glycaemic control on maximally tolerated doses of those oral therapies.

Cost of relevant comparators

Costs below do not include the cost of metformin when drugs are used in combination. Metformin costs approximately £34 a year at a dose of 1500mg per day.

Drug	Dose regimen	Cost per year (£)
Sitagliptin	**100 mg once daily**	**432**
Exenatide	5 to 10 micrograms twice daily	828
Rosiglitazone	4 to 8mg once daily	322 to 660
Pioglitazone	15 to 45mg once daily	314 to 480
Gliquidone	15mg once daily to 60mg three times daily	32 to 383
Repaglinide	0.5mg three times daily to 4mg four times daily	143 to 381
Acarbose	50mg once daily to 200mg three times daily	27 to 304
Nateglinide	60 to 180mg three times daily	257 to 293
Gliclazide MR	30 to 120mg once daily	40 to 160
Glipizide	2.5mg once daily to 10mg twice daily	19 to 149
Glimepiride	1 to 4mg once daily	49 to 138
Tolbutamide	500 to 2000mg daily in divided doses	33 to 133
Gliclazide	40mg once daily to 160mg twice daily	14 to 109
Glibenclamide	5 to 5mg once daily	21 to 63

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2nd July 2007.

Additional information: budget impact

The manufacturer estimated the net budget impact as being £150k in year one rising to £533k by year five. Between 5000 and 6000 patients were assumed to be eligible for treatment with sitagliptin from years one to five. It was assumed that 10% of the year one patients would be treated with sitagliptin rising to nearly 30% by year five. This may be an underestimate based on national horizon scanning estimates and changing clinical practice.

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 17 August 2007.

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.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

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

Nauck MA, Meininger G, Sheng D et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes, Obesity and Metabolism, 2007;9:194-205.

European Medicines Agency (EMEA). European public assessment report (EPAR) for sitagliptin (Januvia). www.emea.europa.eu. Accessed June 2006.