Coventry & Warwickshire

Area Prescribing Committee

Drug Positioning Statement	DPS004
Sitagliptin (Januvia®)	Aug 2012

VERDICT

The Coventry &Warwickshire APC recommends the use of **sitagliptin as the first line dipeptidyl peptidase – 4 (DPP-4) inhibitor where a drug in this class is appropriate in line with NICE Clinical Guideline 87**. For details of the respective properties of the currently available DPP-4 inhibitors please consult the APC approved comparisons chart.

DPP-4 inhibitors are not regarded as specialist drugs and sitagliptin can be initiated in primary care.

Summary notes[1]

INDICATIONS:
Sitagliptin (Januvia®) is licensed for the treatment of type 2 diabetes mellitus:

- as dual therapy: in combination with metformin, or a sulfonylurea (at maximal tolerated dose), or a thiazolidinedione, in patients with insufficient glycaemic control
- as triple therapy: in combination with a sulfonylurea plus metformin, or with metformin plus a thiazolidinedione when dual therapy with these agents does not provide adequate glycaemic control
- as an add on to insulin (with or without metformin) in patients with inadequate glycaemic control
- for restricted 1st line use when diet and exercise do not provide adequate glycaemic control and when metformin is inappropriate due to contra-indications and intolerances

PHARMACOLOGICAL ACTION: Sitagliptin inhibits dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for the inactivation of the incretin hormones, GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). Increasing the endogenous levels of these incretin hormones increases the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion.

PRESENTATION: 25mg, 50mg and 100mg tablets

DOSE: 100mg daily with or without food. When used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycaemia. Moderate renal failure – 50mg daily. Severe renal failure or end stage disease requiring dialysis – 25mg daily.

COST COMPARISON[2] for 28 days supply:

Sitagliptin 100mg daily	£33.26
Saxagliptin 5mg daily	£31.60
Vildagliptin 50mg twice daily	£31.76
Linagliptin 5mg daily	£33.26

Drug profile

Clinical Effectiveness[3,4]

The Midlands Therapeutics Review and Advisory Committee summarised the outcomes of five RCTs, (randomised controlled trials), where sitagliptin was used as add-on therapy. They showed that the addition of sitagliptin to metformin or glimepiride or pioglitazone produced placebo-subtracted mean reductions in HbA1c of 0.51-1.0%. Sitagliptin did not appear to affect body weight. There are no long term data on the effect of sitagliptin on mortality or cardiovascular outcomes[4].

Safety

Adverse effects[1,3] include nasopharyngitis, hypoglycaemia, upper respiratory tract infection, gastrointestinal disturbances, headache and dizziness. The Medicines and Healthcare Regulatory Agency (MHRA) state that **an increased risk of pancreatitis has been identified for all DDP-4 inhibitors**. Reporting rates have ranged between 1/1000 to 1/100. **Patients should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and encouraged to tell their healthcare provider if they have symptoms**[5]**.**
Renal Impairment: In moderate renal impairment (creatinine clearance ≥30-50ml/min), the dose should be reduced to 50mg daily. In severe renal impairment (creatinine clearance <30ml/min), or those with end stage renal disease requiring dialysis, the dose should be reduced to 25mg daily[1].
Hepatic Impairment: No dose change is needed in mild to moderate impairment. No data is available for use in severe impairment.
Elderly: No dose adjustment is required, though limited safety data is available for patients aged ≥75 years,

Current place in therapy

NICE (National Institute for Health and Clinical Excellence)

- In line with clinical guideline 87, sitagliptin can be considered for triple therapy with metformin and a sulfonylurea instead of insulin, if insulin is unacceptable or inappropriate (because of social or recreational issues, injection anxieties, personal issues or obesity).
- The guidelines also recommend that DPP-4 inhibitors can be considered for dual therapy with either metformin or a sulfonylurea when either of these drugs is not tolerated or is contra-indicated or, in the case of sulfonylureas, there is a significant risk of hypoglycaemia.
- Sitagliptin may also be considered for triple therapy, with metformin and a sulfonylurea, in preference to a thiazolidinedione (pioglitazone), if further weight gain with the glitazones would exacerbate or cause significant problems, or if not tolerated or contra-indicated.
- **Sitagliptin should only be continued if there has been a beneficial metabolic response *i.e.* a reduction in HbA1c of at least 0.5 % in 6 months.**

SMC (Scottish Medicines Consortium) [6]

- SMC ID 505/08: Sitagliptin has been accepted for use in combination with a sulfonylurea when metformin is inappropriate, due to contraindications or intolerance, or for use in triple therapy, in combination with sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
- SMC ID 607/10: Sitagliptin monotherapy has been accepted for restricted use in patients for whom both metformin and sulfonylureas are inappropriate due to contraindications or intolerance.
- SMC ID 407/08: Sitagliptin has been approved 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 sulfonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones.

MTRAC (Midlands Therapeutic Review and Advisory Committee)

- Sitagliptin has been deemed suitable for prescribing in primary care, within its licensed indications and according to NICE guidance. There are no long term data on the effect of sitagliptin on mortality or cardiovascular outcomes.

Summary

- Sitagliptin can be considered for dual or triple therapy, (including with insulin), in line with NICE guidelines.
- Sitagliptin should only be continued if there has been a beneficial metabolic response *i.e.* a reduction in HbA1c of at least 0.5 % in 6 months.
- There are no long term data on mortality or cardiovascular outcomes for any of DDP-4 inhibitors.

References

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3. Midlands Therapeutics Review and Advisory Committee. Sitagliptin Verdict & Summary. March 2010. Available from: www.keele.ac.uk/media/keeleuniversity/fachealth/fachealthsop/mtrac/documents/verdict/Sitagliptin.pdf <accessed 13.11.12>
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