



A new class of oral antidiabetic agents is available for prescribing under the brand names Januvia<sup>®</sup> and Galvus<sup>®</sup>. These are respectively: sitagliptin and vildagliptin, and belong to the group known as dipeptidyl peptidase type 4 (DPP-4) inhibitors.

They enhance the levels of active incretin hormones (including glucagon-like peptide 1 [GLP-1]), which are released steadily by the intestine throughout the day and are increased in response to a meal.

Incretin hormones enhance glucose dependant 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. By acting in this way, the actions of gliptins are only used in the presence of food. This prevents any major association with episodes of hypoglycaemia, which can be problematic for some patients on sulphonylureas.

Gliptins are given orally, once a day, and require no dose titration. Both gliptins appear to have a lower propensity for hypoglycaemia and weight gain compared to a sulphonylurea, and are considered to be weight neutral agents.

The SMC has reviewed the evidence and efficacy of sitagliptin (Januvia<sup>®</sup>) and their decision is that it 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. Similar guidance was published for vildagliptin (Galvus<sup>®</sup>), for the treatment of type 2 diabetes mellitus as dual oral therapy in combination with metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.

Vildagliptin is restricted for use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones. It is also licensed for use in combination with sulphonylureas or thiazolidinedione drugs for the treatment of type 2 diabetes, but the SMC has not reviewed either of these combinations.

NICE will review the 'gliptins' and other newer agents for blood glucose control early in 2009. As with all new therapies there is a paucity of outcome data, and realistically treatments such as the gliptins should be reserved only for patients where standard, well established therapy is failing or is inappropriate. Recent safety warnings about glitazones, indicate that until robust safety data is available, these therapies should be used cautiously. Sitagliptin was presented to the LTHT D&T in January 2008, and was supported. Vildagliptin has yet to be assessed by this route.

Joint guidance with respect to Self Monitoring of Blood Glucose (SMBG) in type 2 diabetes has recently been published on the Leeds Health Pathways website, alongside a 'Recommendations and Rationale' document. The document can be found at:  
<http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1212>

## NICE SAFETY UPDATES

NICE guidance has been updated to reflect ongoing safety issues with the glitazones (pioglitazone and rosiglitazone), and their place in therapy. The main safety and action points to consider from the NICE guidance are:

- Warn those prescribed a thiazolidinedione (glitazone) of the possibility of significant oedema and advise on action to take if it develops.
- Do not use a thiazolidinedione in patients who have evidence of heart failure or who are at higher risk of fracture

• When selecting a thiazolidinedione for initiation and continuation of therapy, take into account up-to-date advice from the relevant regulatory bodies (the European

Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost and safety issues (note that only pioglitazone can be used in combination with insulin therapy when initiated and monitored by a specialist).

• **Review all existing patients on a glitazone to ensure treatment is appropriate and within the product license.**

• **Only initiate rosiglitazone in exceptional circumstances.**

• **Pioglitazone is supported locally as the glitazone of choice for new patients where a glitazone is indicated, this was agreed with secondary care physicians at LTHT D&T in January 2008**

It is also worth noting that rosiglitazone and its combination products have recently been added to the updated Leeds Grey List which can be found at: [http://](http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=113)

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## GUIDANCE FOR PRESCRIBING EXENATIDE (Byetta<sup>®</sup>)

Exenatide is an incretin mimetic licensed for the treatment of type 2 diabetes in combination with metformin and/or sulphonylureas in patients who have inadequate glycaemic control on maximally tolerated doses of these drugs. It is available as pre-filled pen cartridges containing 60 doses of either 5 or 10 micrograms. It is given twice daily as a subcutaneous injection.

The most common adverse effects are nausea, vomiting, diarrhoea and hypoglycaemia. Unlike insulin, exenatide is associated with weight loss.

An MHRA Drug Safety Bulletin published in May 2008 has highlights the risk of acute pancreatitis associated with exenatide. The Bulletin makes the following recommendations for healthcare professionals (taken directly from source):

- Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain; back pain may also be present

- If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued

Unlike insulin, exenatide does not require frequent blood glucose monitoring or continued dose titration.

Mortality or morbidity outcome data are not currently available.

Both NICE and the **Scottish Medicines Consortium (SMC)** have reviewed the place in therapy of exenatide. Their decisions are summarised below:

### **NICE Clinical Guideline - Diabetes type 2 update**

Exenatide is not recommended for routine use for people with type 2 diabetes.

It should only be considered for people with type 2 diabetes who have all of the following:

- A body mass index over 35kg/m<sup>2</sup> in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups**

- Specific problems of psychological, biochemical, or physical nature arising from high body weight.**

- Inadequate blood glucose control (HbA1c>7.5%) on conventional oral agent therapy after trial of metformin and sulphonylurea, and where other high cost medications such as a thiazolidinedione or insulin injection therapy would otherwise be started**

NICE also states that exenatide therapy should only be continued if useful metabolic response (at least 1% HbA1c reduction in 6 months and a weight loss of at least 5% at 1 year)

**occurs and is maintained.**

The full guidance can be found here; <http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuidance.pdf>

### **The SMC decision and guidance:**

Exenatide is accepted for restricted use for the treatment of type 2 diabetes mellitus. It should be used 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.

Exenatide was considered by the Leeds Teaching Hospital D&T committee and has been supported for use in line with SMC guidance. This position will be reviewed imminently, with respect to the updated NICE guidance.

**Exenatide has been classed as a 'Green' drug, but we would recommend initiation of therapy is confined to those practitioners with a specialist interest in diabetes or experience of using exenatide.**



## Patient safety tip



### Humulin R 500units in 1ml Insulin

This new product is **FIVE** times the strength of standard insulin. The use of this product carries a **significant risk of death.**



**Drug and Therapeutic Committees support the use of concentrated Humulin R insulin in selected patients. This product is classified as an 'Amber Drug' which requires specialist initiation before transferring prescribing and monitoring into Primary Care.**

**There have been deaths reported in the USA from incorrectly supplying the concentrated 500unit in 1ml product when it was the standard 100 units in 1ml that was required.**

**A poster is being produced locally which will provide information against which to check insulin prescriptions**

### How to contact us

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