Title of Project: NHS Dumfries & Galloway
Type 2 Diabetes Mellitus - Gliptin review
July 2013

1 Aims
• To review all patients receiving treatment with a gliptin to determine if they have had a successful response to treatment (at least 5.5mmol/mol fall in HbA1c at 6 months).
• To offer alternative treatment to those who haven’t responded adequately to a gliptin.

Reason for the review
• NICE recommend that DPP-4 inhibitor therapies (or “gliptins”) are only continued if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_1c in 6 months).\textsuperscript{1} SIGN guidelines 116 also advise to continue treatment with a DPP-4 inhibitor if either the patient’s individualised target is achieved or HbA_1c falls >0.5% [5.5mmol/mol] in 3-6 months.\textsuperscript{2}
• In practice, around 20% of patients treated with a gliptin will see no change or an increase in their HbA1c following initiation of a gliptin.\textsuperscript{3}
• Gliptins, on average cause a 0.6% (7mmol/mol) - 0.7% (8mmol/mol) fall in HbA1c.\textsuperscript{4}
• Metformin and sulphonylureas produce greater reductions in HbA1c than the gliptins and have morbidity and mortality benefits to support their use.
• Optimal glycaemic control is associated with a reduction in microvascular and macrovascular complications in patients with Type 2 diabetes.\textsuperscript{2} Other treatment options, with different modes of action, are available to patients who don’t respond to gliptins.

2 Inclusion Criteria
Search for all patients with a current prescription for one of the following drugs;
• Sitagliptin (Januvia\textsuperscript{®})
• Saxagliptin (Onglyza\textsuperscript{®})
• Vildagliptin (Galvus\textsuperscript{®})
• Linagliptin (Trajenta\textsuperscript{®})
• Metformin + Linagliptin (Jentadueto\textsuperscript{®})
• Metformin + Saxagliptin (Komboglyze\textsuperscript{®})
• Metformin + sitagliptin (Janumet\textsuperscript{®})
• Metformin + vildagliptin (Eucreas\textsuperscript{®})

3 Exclusion Criteria
• Any individual patient exclusions deemed necessary by the GP

4 Preparation and planning
Implementation of the review will be in selected GP practices:
• Protocol to be discussed with all GPs in the practice to ensure that agreement to proceed is reached
• Computer search of all patients prescribed one of the named drugs.
• Review of each patient’s medical notes to identify their current diabetes medication and their respective doses, their HbA1c pre-treatment with a DDP4 inhibitor and at ≥6months post initiation of the DDP4, any previous diabetes medication and the reason for discontinuation.

• Patients with <0.5% (or <5.5mmol/mol) fall in HbA1c six months after initiation of the DDP4 inhibitor to be highlighted to the GP for potential discontinuation of the DDP4 inhibitor. GP to consider initiation of an alternative treatment or up-titration of other diabetes medication. An alternative treatment should be chosen in accordance with the NHS D&G “Treatment Guidance for the Management of Type 2 Diabetes” (see attached) and may include referral for GLP-1 agonist or insulin initiation. Please note that gliptins should not be used in conjunction with a GLP-1 agonist (exenatide/liraglutide) and this is also a reason to discontinue gliptin therapy.

• GP to contact patient regarding change of treatment and rationale.

5 Action

GP to contact patients regarding change of treatment and rationale as above.

GP to complete report, detailing the results of the review for medicines management evidence (see template report).

References:


3. Unpublished data provided by NHS Greater, Glasgow and Clyde


Review to be undertaken by:    GP Authorisation:   Date:
Treatment Guidance for the Management of Type 2 Diabetes
This document should be used in conjunction with the individualising treatment guidance

Aims of Drug Treatment

- To alleviate hyperglycaemic symptoms
- To improve control of glucose and lipids, while avoiding hypoglycaemia
- To avoid excessive weight gain where possible
- To prevent long term complications of diabetes

When to consider tablets

- Type 2 diabetes with inadequate control after at least 12 weeks appropriate diet
- Possibly sooner if symptoms troublesome or if not overweight (BMI < 25)

Avoid in females who are pregnant or planning a pregnancy – refer to secondary care

Dosage Alteration

Changes in dosage should be gradual; in general, dosage adjustments should be made no sooner than at intervals of 8-12 weeks

Target HbA1c

For the majority of patients with diabetes it is accepted that the target HbA1c is 6.5-7.0% (48-53mmol/mol). Some of the more common reasons for setting different targets are discussed further in the guidelines on the individualisation of HbA1c targets. Medications which cause <0.5% (5mmol/mol) fall in HbA1c in 6 months should be discontinued.

Drugs

Metformin

First line agent in overweight individuals and may also be effective for normal weight individuals. Studies suggest may be weight neutral or help with weight loss.

UKPDS showed improvement in cardiovascular and all cause mortality when metformin was used as part of intensive therapy.

It is unlikely to cause hypoglycaemia.

Discontinue Metformin if GFR <30mL/min. Consider dose reduction when GFR falls to <45mL/min.

Contraindicated in acute cardiac / respiratory failure, other severe acute illnesses and chronic alcohol abuse.

GI side effects are experienced in up to 25% of patients, but this can be alleviated by titrating no sooner than every 2 weeks. Only 5% cannot tolerate it. Metformin should be started in low dose and built up gradually in 2 or 3 divided doses to a dose of 1g bd or 850mg bd with or after food, to a usual max of 2g/day. A trial of Metformin MR could be considered in those patients with severe GI side effects who would otherwise discontinue immediate release metformin.
**Sulphonylureas/postprandial glucose regulators**

In general second line to metformin (sulphonylureas are 1st-line in patients with weight loss and osmotic symptoms)

Carries a significant risk of hypoglycaemia

Causes weight gain of 1-2kgs

Can be combined with all other oral agents and insulin

Post prandial regulators (nateglinide/repaglinide) have little outcome data to support their use and are therefore not routinely recommended in Dumfries and Galloway

**Glitazones (thiazolidinediones) - Pioglitazone**

May be an alternative to either Metformin (if not tolerated) or gliclazide (if concern about hypos). Pioglitazone may be used with metformin or a sulphonylurea as dual therapy or with both metformin and a sulphonylurea as triple therapy.

In patients treated with sulphonylureas and metformin, pioglitazone should be considered as an alternative to insulin only when there is fear of insulin, the use of insulin would affect employment or it is anticipated that large insulin doses would be required.

Pioglitazone is licensed in the UK for use with insulin but because of the risk of fluid retention this should only occur in exceptional cases and under close specialist supervision.

Promote average weight gain of 3-4kg

Pioglitazone is contraindicated in patients with a history of heart failure. Patients should be monitored for signs of heart failure; treatment should be discontinued if any deterioration in cardiac status occurs.

Pioglitazone is associated with an increased risk of bladder cancer; pioglitazone should not be used in patients with active bladder cancer, a past history of bladder cancer, or in those with uninvestigated macroscopic haematuria. The risk of bladder cancer increases with age.

Pioglitazone has been associated with an increased risk of fracture, particularly in women. Although the numbers experiencing fractures in the trials is very small, it is recommended that the glitazones be avoided in those with high fracture risk

**Incretin mimetics/DPP-4 inhibitors.**

The incretin hormones (GLP-1, GIP) are produced by the small intestine in response to meals. They act on the pancreas to promote insulin secretion in a glucose–regulated manner. So in effect they are like sulphonylureas, except that they only promote insulin secretion when the glucose is high. The incretins also act centrally to decrease appetite, and they slow gastric emptying causing early satiety and so may help to promote weight loss as well as improve glycaemic control.

Two types of new drug utilise this pathway; GLP-1 mimetics and DPP-4 inhibitors.

- **Incretin mimetics: Exenatide / Liraglutide**

  GLP-1 mimetic which is an injectable agent that lowers HbA1c

  Causes weight loss (approx 4kg on average in 1 year).

  Approved by SMC for use in patients with type 2 diabetes on maximal oral therapy who might otherwise need insulin. Exenatide (Byetta) is also approved for use as an adjunct to basal insulin.
Despite favourable effects on weight and HbA1c there is as yet no outcome data to show reduction in morbidity and mortality.

Individuals who are thought suitable candidates for an incretin mimetic should be referred to secondary care.

In general could be considered for those with a BMI >35 kg/m², with a desire to lose weight, usually <10yrs from diagnosis and in whom addition of insulin therapy will affect employment, in those with a fear of insulin or in those who are deemed likely to require very high insulin doses.

GLP-1 should only be continued where the patient’s HbA1c falls by ≥1% in the first 6 months and their weight falls by ≥5% in the first 12 months.

• **DPP-IV inhibitors Saxagliptin/Sitagliptin**

  DPP-IV breaks down GLP-1 in vivo, so these drugs enhance the effect of naturally produced GLP-1.

  Oral agents but less potent than exenatide or liraglutide. Gliptins are usually stopped when exenatide/liraglutide is started.

  Weight neutral

  The HbA1c reduction seen with these agents is 0.6 – 0.7%; less than is seen with metformin or sulphonylureas. They represent an alternative to other third-line agents such as the glitazones.

  Saxagliptin and Sitagliptin are third-line agents to be used in addition to a SU and/or metformin, or as monotherapy where neither an SU or metformin can be tolerated.

  Sitagliptin should not be used in moderate to severe renal impairment. Saxagliptin can be used in moderate to severe renal impairment at a dose of 2.5mg daily.

  Vildagliptin in non-formulary; it requires additional monitoring and has extra cautions/contraindications (see BNF).

• **Insulin Treatment in type 2 diabetes**

  Please refer to individualising targets information

  - Once daily bedtime nPH insulin (ie Humulin I, Insulatard, Insuman Basal) should be used when adding insulin to metformin and/or sulphonylurea therapy. Basal insulin analogues should be considered only if there are concerns regarding hypoglycaemia risk or difficulty in self administration.
  - Intensifying Insulin Treatment in type 2 Diabetes can achieved by adding prandial insulin-ideally metformin therapy is continued as an insulin sparing therapy and a decision usually made to discontinue SU.
Algorithm for Use of Hypoglycaemic Agents Based on ADA/EASD Consensus statement 2009

After 3 months lifestyle change
Target HbA1c ≤ 7.0%
(53 mmol/mol)

**Metformin**

BMI ≤ 25 kg/m²
consider either Sulphonylurea or Metformin

If GI side-effects limiting

HbA1c ≥ 7.0% (53 mmol/mol) or Metformin intolerant

Consider trial of slow release preparation Metformin MR*

**Well-validated core therapies**

Add Sulphonylurea

HbA1c ≥ 7.5% (59 mmol/mol)

If uncertain consider referral to secondary care

**Less well-validated therapies**

Consider Thiazolidinedione if concerns re: hypoglycaemia with SU OR Consider Gliptin if concerns re: weight gain or hypoglycaemia with SU

INSULIN
Stop TZD but continue SU and Metformin in same dose
Start with basal insulin at bedtime
Analogue insulin should only be used if concerns about hypoglycaemia or problems with self administration
Usually initiated by community DSN

TRIAL ADDITION of TZD
"Triple Oral Therapy"
Stop Gliptin

TRIAL ADDITION of INCRETIN MIMETIC
If BMI > 30
Stop TZD/GLIPTIN
Initiation by specialist team only

Only continue beyond 6/12 if HbA1c reduced by 8 mmol/mol at 6/12 or weight reduced by 5% at 1 year

* If no benefit in GI side effect is seen within 6 months, Metformin MR should be stopped and an alternative agent commenced.
Suggested Report Template

**Aims**
To review all patients receiving treatment with a gliptin to determine if they have had a successful response to treatment (at least 5.5mmol/mol fall in HbA1c at 6 months).
To offer alternative treatment to those who haven’t responded adequately to a gliptin.

**Background**
NICE recommend that DPP-4 inhibitor therapies (or “gliptins”) are only continued if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). SIGN guidelines 116 also advise to continue treatment with a DPP-4 inhibitor if either the patient’s individualised target is achieved or HbA1c falls >0.5% [5.5mmol/mol] in 3-6 months. Around 20% of patients treated with a gliptin will see no change or an increase in their HbA1c following initiation of a gliptin.

**Methods**
An EMIS search was completed to identify all patients who have a current prescription for a gliptin. Patients were assessed for their response to treatment. Patients who did not adequately respond to treatment were considered for an alternative treatment in accordance with NHS D&G “Treatment Guidance for the Management of Type 2 Diabetes.”

**Results**
X patients were identified as having a current prescription for a gliptin.

X of X patients showed a ≥5.5mmol/mol reduction in their HbA1c within 6 months of initiation of a gliptin i.e. had a successful therapeutic response.

X of X patients showed a 0 to 5.5mmol/mol reduction in their HbA1c within 6 months of initiation of a gliptin i.e. a sub-optimal response to treatment.

X of X patients showed a rise in their HbA1c within 6 months of initiation of a gliptin i.e. a sub-optimal response to treatment.

Of those not responding to treatment;

X had their gliptin discontinued

X were referred for GLP-1 therapy
X were referred for insulin
X had doses of their other diabetic medication increased
X had pioglitazone initiated
X had metformin initiated
X had a sulphonylurea initiated

**Conclusion**
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# Gliptin Review - Data Collection Sheet

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<td>HbA1c ≥6months post gliptin initiation (date)</td>
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<td>Points to consider Should gliptin be continued? Alternative treatment indicated? Doses optimisation indicated?</td>
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