TAYSIDE PRESCRIBER

NHS Tayside

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Produced by NHS Tayside Drug and Therapeutics Committee Medicines Advisory Group (MAG)

SPECIAL FOCUS ON DRUGS IN DIABETES

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This bulletin is produced by the Medicines Advisory Group (MAG), which is a sub-group of the NHS Tayside Drug and Therapeutics Committee.

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Introduction

In the last few months there have been quite a number of antidiabetic drugs that have been evaluated by the Scottish Medicines Consortium (SMC) and local advice issued by the Medicines Advisory Group (MAG). This prompted members of the Diabetes Managed Clinical Network (MCN) to review and update formulary choices in Section 6.1 of the NHS Tayside Formulary. The formulary changes were presented to and approved by MAG in June of this year.

The changes were fairly extensive. Much work has gone on behind the scenes to ensure that the formulary, local recommendations and the Tayside Diabetes Handbook were updated to reflect these changes. We have collated the information and summarised the changes in this Supplement. We hope you find this information useful.

Rosiglitazone and Cardiovascular Risk

Following new evidence showing increased cardiovascular risk with rosiglitazone compared to pioglitazone highlighted in a recent MHRA safety alert (26th July 2010), **rosiglitazone** is **not recommended** for use within NHS Tayside. There is currently an ongoing Europe-wide review of the risks and benefits of rosiglitazone due to these concerns. Further information can be found on the MHRA website. In Tayside, patients who are currently treated with rosiglitazone should be gradually changed to pioglitazone.

Doses recommended for conversion by the NHS Tayside Diabetes MCN are as follows:

- Rosiglitazone 4mg tablets to pioglitazone 30mg tablets
- Rosiglitazone 8mg tablets to pioglitazone 45mg tablets
- Avandamet® 2mg/1g tablets to Competact® 15mg/850mg tablets (Note: metformin dose reduction)

Doses of pioglitazone should be adjusted according to response.

NHS Tayside Formulary: Updates to Section 6.1- Drugs used in Diabetes

Following the June meeting of MAG, the following changes have been made to Section 6.1 Drugs used in diabetes within the Formulary

Sulphonylureas

- Addition of a link to: SIGN guideline No 116 - Management of diabetes.
- Addition of **glibenclamide** to formulary - restricted to use in women with gestational diabetes. Information on use of metformin or glibenclamide in gestational diabetes has also been added in line with recommendations from SIGN No 116.

Biguanides

- Addition of **metformin hydrochloride prolonged release tablets (Glucophage® SR)** to formulary - restricted to use in patients who are intolerant of immediate release metformin (due to severe GI side-effects) and in whom the prolonged release tablet allows the use of a dose not previously tolerated.

Thiazolidinediones

Thiazolidinediones are 2nd or 3rd line treatment options in type 2 diabetes. They may be added to metformin and sulphonylurea therapy, or substituted for either in cases of intolerance.[I]

- **Pioglitazone▼** is now the 1st line choice of thiazolidinedione in Tayside. Pioglitazone ▼may also be used as monotherapy for patients in whom sulphonylureas are contraindicated or not tolerated and in whom consideration is otherwise being given to commencing insulin therapy. Pioglitazone ▼may be combined with insulin under close specialist supervision in patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance. Addition of **pioglitazone 15mg / metformin 850mg Competact®▼)** to formulary - restricted to use in patients who cannot be treated with a sulphonylurea in combination with metformin.
- **Rosiglitazone** is not recommended for use within NHS Tayside. This is following new evidence showing increased cardiovascular risk with rosiglitazone compared to pioglitazone highlighted in a recent MHRA safety alert. **Avandamet®▼(rosiglitazone / metformin)** has been removed from formulary.

DPP-4 inhibitors (or gliptins)

DPP-4 inhibitors (or **gliptins**) are 2nd or 3rd line treatment options in type 2 diabetes.

Sitagliptin ▼ is now the 1st line choice of DPP-4 inhibitor in Tayside.

Sitagliptin may be used:

- as monotherapy in patients for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.
- in combination with metformin when a sulphonylurea is not appropriate.
- in combination with a sulphonylurea when metformin is not appropriate.
- in combination with both a sulphonylurea and metformin when dual therapy does not provide adequate glycaemic control.

- Addition of **sitagliptin 50mg / metformin 1000mg (Janumet®▼)** to formulary - restricted to use in patients for whom this combination is an appropriate choice of therapy either when the addition of sulphonylureas to metformin monotherapy is not appropriate or in combination with a sulphonylurea (triple combination therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and sulphonylurea.
- Removal of **vildagliptin ▼** and **vildagliptin / metformin (Eucreas®▼)** from formulary.
- Addition of **saxagliptin ▼** to formulary - restricted to use as add-on combination therapy with metformin when metformin alone does not provide adequate glycaemic control and where the addition of a sulphonylurea is not appropriate.

Incretin mimetics

- Addition of **liraglutide ▼** to formulary and change of local recommendation for **exenatide ▼**. Both are now formulary entries - restricted to initiation by secondary care as a third line antidiabetic agent. (GPs may prescribe under the direction of the diabetic clinic).

REFERENCES

[I] Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. Edinburgh: SIGN; 2010. (SIGN publication no. 116). Available from: [http://www.sign.ac.uk/pdf/sign116.pdf]

Changes to local recommendations of SMC advice for diabetic drugs

The table below lists the changes to previous local recommendation categories for diabetic drugs that have been accepted for use in NHS Scotland by the SMC. These changes are also reflected within the NHS Tayside Diabetes MCN website Handbook under 'Pharmacological management of type 2 diabetes'

Medicine	Indication	Previous local recommendation category	New local recommendation category
Metformin hydrochloride prolonged release tablets 500mg, 750mg, 1000mg (Glucophage SR®) *-2nd Re-submission*	Restricted use for the treatment of Type 2 diabetes mellitus in patients who are intolerant of immediate release metformin and in whom the prolonged release tablet allows the use of a dose not previously tolerated or in patients for whom a once daily preparation offers a clinically significant benefit.	**Non formulary**	**Formulary - restricted use** Restricted to use in patients who are intolerant of immediate release metformin (due to severe GI side-effects) and in whom the prolonged release tablet allows the use of a dose not previously tolerated.
Pioglitazone (Actos®) *- Full submission*	Triple therapy in type 2 diabetes.	**Formulary (prescribing note)** (Tayside Diabetes MCN advice March 2007 - In type 2 diabetics with BMI of 27 and over sulphonylurea / metformin / glitazone triple therapy is recommended prior to the use of insulin in patients unable to achieve glycaemic control on dual combination therapy).	**Formulary – 1st line choice of thiazolidinedione** (Thiazolidinediones are 2nd or 3rd line treatment options in type 2 diabetes)
Pioglitazone (Actos®) *- Re-submission*	Restricted use as monotherapy for type 2 diabetes mellitus in whom consideration is otherwise being given to commencing insulin therapy. It is not recommended as monotherapy for any other group of patients. Its use should be restricted to patients who have already experienced severe hypoglycaemia or patients in whom metformin and sulphonylureas are contra-indicated or not tolerated.	**Recommended within specialist treatment pathway (GPs may prescribe under the direction of the diabetes clinic)** (Tayside Diabetes MCN advice March 2007-In type 2 diabetics with BMI of 27 and over glitazone monotherapy is recommended in patients in whom metformin is contraindicated).	**Formulary – 1st line choice of thiazolidinedione** Thiazolidinediones are 2nd or 3rd line treatment options in type 2 diabetes)
Pioglitazone (Actos®) *- Full submission*	Type 2 diabetes mellitus in combination with insulin.	**May be prescribed under the direction of the Diabetes Clinic**	**May be prescribed under the direction of the Diabetes Clinic**
Pioglitazone/metformin (Competact®) *- Abbreviated submission*	Restricted use for the treatment of type 2 diabetes mellitus in 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.	**Non-formulary** (Tayside Diabetes MCN advice March 2007- In type 2 diabetics with BMI of 27 and over glitazone/ metformin dual combination therapy is recommended in patients unable to achieve glycaemic control on monotherapy).	**Formulary - restricted use** Use is restricted to patients who cannot be treated with a sulphonylurea in combination with metformin.
Rosiglitazone (Avandia®) *- Re-submission*	Rosiglitazone (Avandia®) is accepted for restricted use within NHS Scotland as monotherapy for type 2 diabetes mellitus patients in whom consideration is otherwise being given to commencing insulin therapy. **It is not recommended as monotherapy for any other group of patients.** Its use should be confined to patients who have already experienced severe hypoglycaemia or who are intolerant of metformin and sulphonylureas.	**Recommended within specialist treatment pathway** (Tayside Diabetes MCN advice March 2007 - In type 2 diabetics with BMI of 27 and over glitazone monotherapy is recommended in patients in whom metformin is contraindicated).	**Not recommended in Tayside**

Changes to local recommendations of SMC advice for diabetic drugs (continued…)

Medicine	Indication	Previous local recommendation category	New local recommendation category
Rosiglitazone maleate/metformin hydrochloride (Avandamet®) *- Abbreviated submission*	New formulation of existing combination Rosiglitazone maleate/metformin hydrohloride (Avandamet®) in the under-noted formulations is accepted for use in NHSScotland for the treatment of Type 2 diabetes mellitus in patients for whom a combination of rosiglitazone and metformin is appropriate. The new formulations facili-tate dosage adjustment and, at a given dose combination, are not associated with increased cost compared with existing formulations. As previously stated by SMC (February 2004), (Rosiglitazone maleate 2mg and metformin hydrochloride 1000mg). (Rosiglitazone maleate 4mg and metformin hydrochloride 1000mg).	**Formulary (prescribing note - May be prescribed for those patients already receiving rosiglitazone and metformin separately and for whom a combination product would be preferable)** (Tayside Diabetes MCN advice March 2007- In type 2 diabetics with BMI of 27 and over, glitazone/ metformin dual combination therapy is recommended in patients unable to achieve glycaemic control on monotherapy).	**Not recommended in Tayside**
Rosiglitazone (Avandia®) *- Abbreviated submission*	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.	**Recommended within specialist treatment pathway (GPs may prescribe under the direction of the diabetic clinic)** (Tayside Diabetes MCN advice March 2007 - In type 2 diabetics with BMI of 27 and over sulphonylurea/metformin/glitazone triple therapy is recommended prior to the use of insulin in patients unable to achieve glycaemic control on dual combination therapy).	**Not recommended in Tayside**
Rosiglitazone / metformin tablet (Avandamet®) *-Abbreviated submission*	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.	**Formulary (prescribing note)** Locally, rosiglitazone / metformin / sulphonylurea triple therapy should be initiated by the diabetes clinic or by GPs experienced in the treat-ment of diabetes. (Tayside Diabetes MCN advice March 2007 - In type 2 diabetics with BMI of 27 and over sulphonylurea/metformin/glitazone triple therapy is recommended prior to the use of insulin in patients unable to achieve glycaemic control on dual combination therapy).	**Not recommended in Tayside**
Saxagliptin 5mg film-coated tablet (Onglyza®) *- Full submission*	Treatment of adult patients with type 2 diabetes mellitus as add-on combination therapy with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.	**Non Formulary** Restricted to use in patients only when the addition of sulphonylureas is not appropriate, and represents an alternative to other agents such as thiazolidinediones.	**Formulary – restricted use** Restricted to use as add-on combination therapy with metformin, when metformin alone does not provide adequate glycaemic control and only in patients when the addition of a sulphonylurea is not appropriate.
Sitagliptin 100mg film-coated tablet (Januvia®) *- Full submission*	As monotherapy, to improve glycaemic control in patients with type 2 diabetes mellitus who are inadequately con-trolled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance .	**Awaiting update of Formulary section 6.1 – Drugs used in diabetes**	**Formulary – 1st line choice of gliptin (DPP-4 inhibitor)** (DPP-4 inhibitors are 2nd or 3rd line treatment options in type 2 diabetes)
Sitagliptin 100mg tablets (Januvia®) *- Full submission*	Type 2 diabetes in combination with metformin.	**Formulary** Alternative to the addition of a glitazone in patients unsuitable for treatment with sulphonylureas	**Formulary – 1st line choice of gliptin (DPP-4 inhibitor)** (DPP-4 inhibitors are 2nd or 3rd line treatment options in type 2 diabetes)

Changes to local recommendations of SMC advice for diabetic drugs (continued…)

Medicine	Indication	Previous local recommendation category	New local recommendation category
Sitagliptin 100mg tablets (Januvia®) *- Full submission*	Patients with type 2 diabetes mellitus to improve glycaemic control in combination with a sulphonylurea with or without metformin.	**Formulary**	**Formulary – 1st line choice of gliptin (DPP-4 inhibitor)** (DPP-4 inhibitors are 2nd or 3rd line treatment options in type 2 diabetes)
Sitagliptin 50 mg and metformin hydrochloride 1000 mg (Janumet®) 50/1000 *- Abbreviated submission*	As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of sitagliptin and metformin.	**Non Formulary** Restricted to use in patients for whom a combination of sitagliptin and metformin is an appropriate choice of therapy and only when the addition of sulphonylureas to metformin monotherapy is not appropriate. Sitagliptin represents an alternative to other agents such as thiazolidin-ediones.	**Formulary – restricted use** Restricted to use in patients for whom a combination of sitagliptin and metformin is an appropriate choice of therapy either when the addition of sulphonylureas to metformin monotherapy is not appropriate or in combination with a sulphonylurea (triple combination therapy) in patients nadequately controlled on their maximal tolerated dose of metformin and sulphonylurea.
Sitagliptin 50 mg and metformin hydrochloride 1000 mg (Janumet®) 50/1000 *-Abbreviated submission*	In combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.	Not applicable (SMC advice published on 9th August 2010)	**Formulary – restricted use** Restricted to use in patients for whom a combination of sitagliptin and metformin is an appropriate choice of therapy either when the addition of sulphonylureas to metformin monotherapy is not appropriate or in combination with a sulphonylurea (triple combina-tion therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and sulphonylurea.
Vildagliptin 50mg tablets (Galvus®) *- Full submission*	Type 2 diabetes mellitus as dual therapy in combination with metformin.	**Formulary** Alternative to the addition of a glitazone in patients unsuitable for treatment with sulphonylureas.	**Non-formulary**
Vildagliptin 50mg tablets (Galvus®) - Full submission	Type 2 diabetes mellitus as dual oral therapy in combination with a sulphony-lurea in patients with insufficient glycae-mic control despite maximal tolerated dose of a sulphonylurea or for whom metformin is inappropriate due to contra-indications or intolerance.	**Non formulary for this indication**	**Non-formulary**
Vildagliptin/metformin (Eucreas®) *- Abbreviated submission*	Type 2 diabetes mellitus patients.	**Formulary** Alternative to the addition of a glitazone in patients unsuitable for treatment with sulphonylureas.	**Non-formulary**

Changes to local recommendations of SMC advice for diabetic drugs (continued…)

Medicine	Indication	Previous local recommendation category	New local recommendation category
Exenatide inj (Byetta®) *-Full submission*	Type 2 diabetes mellitus in combination with metformin and/or sulphonylurea.	**GPs may prescribe under the direction of the Diabetic Clinic** Locally, exanatide sc injection is restricted to type 2 diabetic patients who have failed to achieve glycaemic control on metformin and/or sulphonylureas and in whom glitazones are unsuitable (eg due to heart failure, hepatic impairment or where rapid glycaemic control is required) and who would otherwise move to insulin therapy. Treatment should be under the direction of the diabetic clinic.	**Formulary – restricted use** *Restricted to initiation by secondary care as a third line antidiabetic agent.* (GPs may prescribe under the direction of the diabetic clinic) (Liraglutide is preferred over exenatide)
Liraglutide 6mg/mL prefilled pen for injection (3mL) (Victoza®) *- Full submission*	Restricted use as a third line agent for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control. • in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea • in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.	**Non formulary** **GPs may prescribe under the direction of the Diabetic Clinic** Third line anti-diabetic agent for glycaemic control.	**Formulary – restricted use** *Restricted to initiation by secondary care as a third line antidiabetic agent.* (GPs may prescribe under the direction of the diabetic clinic) (Liraglutide is preferred over exenatide)