NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 15 **September 2010**

SUSPENSION OF MARKETING AUTHORISATION OF ROSIGLITAZONE

Summary

- **The marketing authorisations of rosiglitazone containing medicines (Avandia and Avandamet) have been suspended and both products will soon be unavailable.**
- **All patients currently taking either of these products will need to be reviewed and their treatment changed.**
- **In many cases, a straightforward switch to pioglitazone or the pioglitazone/metformin combination product (Competact) should be sufficient, although prescribers are reminded of NICE Clinical Guideline 87 on the management of type 2 diabetes (May 2009) which offers a wider range of alternatives including DPP-4 inhibitors (gliptins), repaglinide, nateglinide, acarbose, exenatide and insulin therapy.**
- **Pioglitazone is not a recommended alternative where further weight gain would cause or exacerbate significant problems associated with high body weight, where pioglitazone is contraindicated, where the patient is at increased fracture risk or where the person has had an unsatisfactory response to a glitazone in the past. It is anticipated that most patients currently taking rosiglitazone will not fall into any of these categories.**
- **Where risk of weight gain or fracture, contra-indication or unsatisfactory response to a glitazone is identified, a dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptin) should be considered as an alternative**.
- **At present, pioglitazone is judged to be a safer alternative to rosiglitazone in terms of cardiovascular safety, although further studies are required to confirm or refute this.**
- **The DPP-4 inhibitors (gliptins) are not necessarily safer alternatives to glitazones. The PACEF assessment of all three of the existing agents (sitagliptin, vildagliptin and saxagliptin) has raised concerns over lack of long-term safety data and lack of outcomes data.**
- **Pioglitazone (Actos) is due for patent expiry in January 2011 after which lower cost generic preparations are likely to become available; all of the gliptins have been licensed relatively recently and will have much longer patent lives.**
- **Patients currently receiving rosiglitazone and insulin combination therapy should be reviewed by a specialist to determine appropriate alternative therapy.**

Introduction

Following a Europe-wide review of available data on the risks and benefits of medicines containing rosiglitazone (Avandia, Avandamet), the UK Commission on Human Medicines (CHM) has concluded that there is an increased cardiovascular

risk for this medicine [1].The European Committee on Medicinal Products for Human Use (CHMP) announced on 23rd September that it is recommending the suspension of the marketing authorisations of rosiglitazone across the European Union [2].

The following advice has been issued:

- Prescribers should put in place a system to ensure that all patients are reviewed and changed to another suitable treatment in line with NICE recommendations.
- While this change could happen at the next routine appointment, prescribers may wish to see patients sooner rather than later in order to reduce patient anxiety.
- Patients who are concerned should not stop their treatment but should contact the healthcare professional supervising their diabetic treatment.
- Pharmacists should be aware that rosiglitazone-containing medicines will soon no longer be available. They should advise patients presenting with a prescription for Avandia or Avandamet to speak to their doctor to arrange a review.

Rosiglitazone will cease to be available in Europe within the next few months. The European suspension will remain in place unless the marketing authorisation holder can provide convincing data to identify a group of patients in whom the benefits of the medicine outweigh the risks.

What should be prescribed as an alternative to rosiglitazone?

Standard PACEF advice and the advice of local diabetologists issued in August 2009 recommended that there should be no new initiations of rosiglitazone and that pioglitazone should be the preferred glitazone of choice [3]. In response to this, many practices reviewed their use of glitazones and, following individual review, changed many patients over to pioglitazone. Following on from the suspension of marketing authorisation of rosiglitazone, it is recommended that all remaining patients taking Avandia or Avandamet (the rosiglitazone/metformin combination product) should be reviewed and changed to alternative therapy. **In many cases, a straightforward switch to pioglitazone or the pioglitazone/metformin combination product (Competact) should be sufficient, although prescribers are reminded of relevant NICE guidance as published in Clinical Guideline 87 on the management of type 2 diabetes (May 2009) [4].**

NICE recommend glitazone/ metformin combination therapy as an alternative to metformin/sulphonylurea combination therapy where blood glucose control is inadequate and the person is at significant risk of hypoglycaemia or its consequences or in certain social circumstances (e.g. living alone) or a sulfonylurea is contraindicated or not tolerated. Within this context, glitazones are seen as a way of mitigating the risk of hypoglycaemia associated with sulfonylureas.

According to NICE advice, glitazones may be preferable to dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) if: (1) the person has marked insulin insensitivity; (2) a DPP-4 inhibitor is contraindicated; or (3) the person has previously had a poor response to a DPP-4 inhibitor. Where either a DPP-4 inhibitor or a glitazone is suitable, the choice of treatment should be based on patient preference.

When switching from rosiglitazone to pioglitazone, what are the equivalent doses?

Current rosiglitazone dose	Current HbA1c	Suggested initial pioglitazone dose
4mg daily	< 7.5%	15mg daily
4mg daily	> 7.5%	30mg daily
8mg daily	< 7.5%	30mg daily
8mg daily	> 7.5%	45mg daily

When would a straightforward switch to pioglitazone not be appropriate?

(1) Where further weight gain would cause or exacerbate significant problems associated with high body weight;
(2) Where pioglitazone is contraindicated (i.e. hypersensitivity to the active substance or to any of the excipients, cardiac failure or history of cardiac failure (NYHA stages I to IV), hepatic impairment)
(3) Where the person has had an unsatisfactory response to a glitazone in the past.
(4) Where the patient is at increased fracture risk. The FRAX assessment tool is a useful way of assessing fracture risk when considering a glitazone (www.shef.ac.uk/FRAX/tool.jsp)

In most cases, patients currently taking rosiglitazone should not fall into any of these categories. **However, where risk of weight gain or fracture, contra-indication or unsatisfactory response to a glitazone is identified, a dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptin) should be considered as an alternative**. Prescribers are advised that sitagliptin (Januvia) and sitagliptin/metformin (Janumet) are the only DPP-4 inhibitor formulations currently approved for use in Lincolnshire.

How safe is pioglitazone in comparison to rosiglitazone?

A recent study in the *British Medical Journal* compared the risk of acute myocardial infarction (MI), heart failure and death in patients with type 2 diabetes treated with pioglitazone or rosiglitazone [5]. In this retrospective cohort study, it was found that over the 6-year study period significantly fewer patients reached the primary composite endpoint of death or hospital admission for acute MI or heart failure with pioglitazone compared to rosiglitazone (5.3% vs 6.9%). In terms of absolute risk this was estimated to equate to one additional composite event each year for every 93 patients treated with rosiglitazone rather than pioglitazone.

In addition, the PROactive study which compared pioglitazone to placebo found no significant difference in the primary endpoint, a composite of all cause mortality, non-fatal MI, stroke, acute coronary syndrome, vascular interventions or amputation [6].

A review of these studies in *MeReC Rapid Review* (September 2009) concluded that these results are interesting, but cautioned against over interpretation of observational data [7]. At present, pioglitazone is judged to be a safer alternative to rosiglitazone in terms of cardiovascular safety, although further studies are required to confirm or refute this.

In addition to cardiovascular safety, the recently published *MeReC Stop Press* bulletin (September 2010) emphasizes the increased fracture risk with both rosiglitazone and pioglitazone and the American Food and Drugs Administration

(FDA) ongoing review or a ten-year epidemiological study investigating the possible association between pioglitazone and bladder cancer [8].

Are DPP-4 inhibitors safer alternatives to pioglitazone?

Not necessarily. DPP-4 inhibitors (gliptins) are a relatively new group of drugs; the PACEF assessment of all three of the existing agents (sitagliptin, vildagliptin and saxagliptin) raised concerns over lack of long-term safety data and lack of outcomes data [3]. In addition, a Cochrane review has identified an increase in all-cause infections with DPP-4 inhibitors and recommended that their use should be avoided in patients with a history of recurrent urinary tract infections. DPP-4 inhibitors contribute to T-cell activation which can compromise immune function; the long-term consequences of this remain to be fully investigated. In addition, vildagliptin is contra-indicated in congestive heart failure (NYHA class III-IV) and should only be prescribed with caution in CHF NYHA class I-II. As a result, vildagliptin cannot be seen as a safer alternative to glitazones in patients suffering from cardiac failure or with a history of cardiac failure. There have also been rare reports of hepatic dysfunction associated with vildagliptin; monitoring of Liver Function Tests (LFTs) at 3 monthly intervals in the first year and periodically thereafter is recommended by the manufacturers.

What about patients taking rosiglitazone and insulin combination therapy?

Patients currently receiving rosiglitazone and insulin combination therapy may require specialist advice or review to determine appropriate alternative therapy.

In the wake of the rosiglitazone withdrawal, what are the recommended Lincolnshire alternatives?

The following table summarizes the Traffic Light status of all of the currently available glitazones and gliptins. The preferred products are highlighted in bold:

Drug	Indication(s)	Traffic Light Status
Pioglitazone tablets 15mg, 30mg, 45mg (Actos) **Pioglitazone/metformin tablets 15mg/850mg (Competact)**	**Licensed as monotherapy for type 2 diabetes, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate.** **Dual oral therapy in combination with metformin particularly in overweight patients, or in combination with a sulfonylurea in patients with an intolerance or contraindication to metformin, for type 2 diabetes inadequately controlled by maximal tolerated doses of either metformin or sulfonylurea.** **Triple oral therapy in combination with metformin and a sulfonylurea, particularly in overweight patients, for type 2 diabetes inadequately controlled by dual therapy with metformin or a sulfonylurea.** **Combined with insulin in type 2 diabetes inadequately controlled by insulin in patients with an intolerance or contraindication to metformin.**	**GREEN**
Rosiglitazone tablets 4mg, 8mg (Avandia)	Licensed as monotherapy for type 2 diabetes, particularly overweight patients, inadequately controlled by	RED-RED No new initiations; all existing patients should be reviewed and

	diet and exercise for whom metformin is inappropriate. Dual oral therapy with metformin particularly in overweight patients, or with a sulfonylurea in patients with an intolerance or contraindication to metformin, for type 2 diabetes inadequately controlled by maximal tolerated doses of either metformin or sulfonylurea. Triple therapy with metformin and a sulfonylurea, particularly in overweight patients, for type 2 diabetes inadequately controlled by dual therapy.	changed to alternative therapy
Rosiglitazone/metformin tablets 2mg/500mg, 2mg/1000mg, 4mg/1000mg (Avandamet)	Licensed for type 2 diabetes, particularly overweight patients, inadequately controlled by maximal tolerated doses of metformin or in triple therapy with a sulfonylurea, inadequately controlled by maximal tolerated doses of metformin and a sulfonylurea.	RED-RED No new initiations; all existing patients should be reviewed and changed to alternative therapy
Saxagliptin tablets 5mg (Onglyza)	Licensed for the treatment of type 2 diabetes mellitus (DM), either in combination with metformin or a sulfonylurea or a thiazolidinedione (glitazone) when monotherapy with these alternative agents (in combination with diet and exercise) does not provide adequate glycaemic control.	RED-RED
Sitagliptin tablets 100mg (Januvia)	**Licensed for dual therapy with metformin or a glitazone for type 2 diabetes inadequately controlled by diet, exercise and either metformin or a glitazone alone; or with a sulfonylurea in patients with an intolerance or contraindication to metformin, inadequately controlled by maximal tolerated doses of sulfonylurea alone. Also licensed for triple therapy with metformin and a sulfonylurea for type 2 diabetes inadequately controlled by dual therapy.**	**GREEN N.B. Can be considered at step two in combination with either metformin or a sulfonylurea. Can also be considered at step three in combination with metformin and a sulfonylurea (see text for details).**
Sitagliptin/Metformin 50mg/1000mg tablets (Janumet)	**Licensed as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus inadequately controlled on their maximal dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. Licensed for triple therapy in combination with either a sulphonylurea or thiazolidinedione (glitazone); also licensed for use with insulin.**	**GREEN**
Vildagliptin tablets 50mg (Galvus)	Licensed for the treatment of type 2 diabetes in combination with: (1) metformin, in patients inadequately controlled by maximal tolerated dose of metformin alone; (2) a sulfonylurea, in patients with an intolerance or contraindication to metformin inadequately controlled by maximal tolerated dose of sulfonylurea; (3) a glitazone, in patients with insufficient glycaemic control and for whom the use of glitazone is appropriate	RED-RED
Vildagliptin/metformin tablets	Licensed for the treatment of type 2	RED-RED

50mg/850mg and 50mg/1000mg (Eucreas)	diabetes in patients inadequately controlled by maximal tolerated dose of metformin alone or who are already treated with the combination of vildagliptin and metformin prescribed separately	

What are the implications of cost differences and patent expiries?

Preferred products are highlighted in bold. Pioglitazone (Actos) is due for patent expiry in January 2011 after which lower cost generic preparations are likely to become available; all of the gliptins have been licensed relatively recently and will have much longer patent lives.

Drug	Dose	28 day cost
Pioglitazone tablets (Actos)	**15mg to 45mg once daily**	**£25.83 to £39.55** **Patent expiry is due in January 2011**
Pioglitazone/metformin tablets 15mg/850mg (Competact)	**One twice daily**	**£35.89**
Saxagliptin tablets 5mg (Onglyza)	5mg once daily	£31.60
Sitagliptin tablets 100mg (Januvia)	**100mg once daily**	**£33.26**
Sitagliptin/metformin tablets 50mg/1000mg (Janumet)	**One twice daily**	**£34.56**
Vildagliptin tablets 50mg (Galvus)	50mg once daily (with a sulfonylurea) 50mg twice daily (with metformin or pioglitazone)	£15.88 to £31.76
Vildagliptin/metformin 50mg/850mg, 50mg/1000mg (Eucreas)	One twice daily	£29.64

Priced quoted from *MIMS* September 2010

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27th September 2010