The Association for British Clinical Diabetologists: recommendations following suspension of rosiglitazone (Avandia)

On 23 September 2010, the European Medicine's Agency (EMA) Committee on Medicinal Products for Human Use (CHMP) recommended the suspension of marketing authorisation for Avandia (rosiglitazone) and Avandamet (rosiglitazone/metformin) as it was felt that the risks of this treatment outweighed the benefits. The chair of the Commission on Human Medicines (CHM) has written to health care professionals to inform them of the advice of the CHM following this Europe-wide review.[1]

There have been concerns about a possible increase in cardiovascular events in patients treated with rosiglitazone since 2007 when a meta-analysis of 42 separate studies involving rosiglitazone was published in the *New England Journal of Medicine*.[2] This found that subjects who had been allocated rosiglitazone had a significant increase in the risk of myocardial infarction and an increase in the risk of death from cardiovascular disease. It was well known that the thiazolidinedione (TZD) class of drugs caused fluid retention and oedema.[3] As a result of this TZDs could exacerbate pre-existing heart failure and therefore were already contraindicated in this group of patients. However, the suggestion that rosiglitazone caused adverse cardiovascular outcomes outside of this known contraindication was of concern.

GlaxoSmithKline, the manufacturer of rosiglitazone, disagreed strongly with the findings in this paper and has argued that the RECORD study (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes) has shown no evidence of cardiovascular harm.[4] However, significant concerns have been raised regarding the design and conduct of this study.[5]

Although a few retrospective case control database studies have suggested equivalent cardiovascular risk for pioglitazone,[6] there is superior evidence in the form of a large-scale, multicentre, randomised control study (PROactive) which studied the cardiovascular effects of pioglitazone.[7] Although the primary endpoint of this trial did not show significant benefit, this was associated with increased interventions for peripheral vascular disease and this study found that treatment with pioglitazone did significantly reduce the secondary composite endpoint of myocardial infarction, stroke or all-cause mortality. It should be noted that the individuals recruited to this study were all patients with type 2 diabetes with evidence of pre-existing vascular disease (i.e. a very high risk group of patients). Therefore, there is reasonable evidence that pioglitazone does not cause adverse cardiovascular outcomes outside the known contraindication of heart failure. Reassuringly, these findings are supported by meta-analysis data suggesting that pioglitazone offers some protection against cardiovascular disease.[8]

Summary

- For all new prescriptions of thiazolidinediones, pioglitazone must be used
- Patients already taking rosiglitazone should have a medication review in order to consider alternative therapy
- Replacement therapy should be tailored according to the clinical needs of the individual patient and should be in line with existing NICE guidance when possible. Those patients whose glycaemic control requires consideration of alternatives to sulphonylureas and metformin should have an assessment of cardiovascular risk status, heart failure, osteoporosis fracture risk, weight, hepatic and renal function, hypoglycaemia and pancreatitis risk
- Patients already taking rosiglitazone who do not wish to change to alternative therapy should be advised that it is not possible to continue rosiglitazone as this therapy has been suspended and will be withdrawn
- Prior evidence of heart failure or impairment of left ventricular function remains a strict contraindication for the use any thiazolidinediones. Osteoporosis and previous fracture may also be considered a contraindication to a thiazolidinedione

It is essential that any treatment for type 2 diabetes has demonstrated cardiovascular safety (even if not cardiovascular benefit). There is evidence that good glycaemic control using older treatments such as metformin, sulphonylureas and insulin results in a reduction of microvascular complications and is safe from the cardiovascular standpoint.[9,10] It should also be noted that, to date, the newer alternative comparator therapies such as the DPP-IV inhibitors or GLP-1 mimetics have no published cardiovascular safety data from controlled trials.

ABCD recommendations

The following recommendations should be read in conjunction with Table 1. The Association for British Clinical Diabetologists (ABCD) recommends that:

- Patients currently taking rosiglitazone should be switched to an alternative medication. This should be done via a medication review which provides a useful opportunity to reassess the patient's diabetes management as a whole. Options for switching are summarised in Table 1.
- The choice of drug should depend on the current concomitant medication and the individual needs of the patient. The risks and benefits of each therapy should be discussed with the patient prior to switching.

• Replacement therapy should be consistent with existing National Institute for Health and Clinical Excellence (NICE) guidance (CG87) when possible.[11]
• Cautions, contraindications and up-to-date guidance from the MHRA (Medicines and Healthcare products Regulatory Agency) should be taken into account prior to prescribing.
• Careful consideration should be made prior to switching patients to alternative newer therapies (such as GLP-1 mimetics and DPP-IV inhibitors) which also do not have published cardiovascular safety data from controlled trials.
• Note that risk of pregnancy should be taken into account. Women of child-bearing age should not be

Table 1. Options for switching from rosiglitazone (in order of preference)

Order of preference	Switch to	Advantages and disadvantages	Type of patient who may benefit and how to switch
1	Nothing (i.e. simply stop rosiglitazone)	Cheapest option. No side effects	Patients who have very tight glycaemic control, i.e. HbA_{1c} <6.5% (48mmol/mol) on rosiglitazone. Note that this may result in loss of glycaemic control, and HbA_{1c} should be reviewed within 2 months
2	Replace with metformin (if not already on metformin)	Cost-effective. Consistent with NICE guidance (CG87). Established and effective drug	Should be the preferred choice for patients who are able to tolerate metformin and have no contraindication to its use *Stop rosiglitazone and then start metformin 500mg after meals once a day and titrate. People experiencing limiting GI side effects may tolerate the slow release formulation*
3	Replace with sulphonylurea (if not already on sulphonylurea [SU])	Cost-effective. Consistent with NICE guidance (CG87). Established and effective drug. Risk of hypoglycaemia. Risk of weight gain	Likely to be suitable for many patients currently on rosiglitazone as long as they have not had previous hypoglycaemia with SU therapy *Stop rosiglitazone and then start gliclazide 40mg bd or another SU about 4 weeks later. Titrate according to response*
4	Replace with pioglitazone	Straight swap of thiazolidinedione (TZD) for TZD. Remaining risk of oedema and fractures	Suitable for patients who have previously responded very well to rosiglitazone. Caution in post-menopausal women (consider DEXA scan prior) *Stop rosiglitazone and start pioglitazone according to recommended titration algorithm* (see Table 2)
5=	DPP-IV inhibitors (if not already on DPP-IV inhibitor)	Negligible risk of hypoglycaemia. Weight-neutral. No cardiovascular safety evidence	May be suitable for some patients in whom weight gain may be particularly undesirable (in line with NICE CG87 guidance) *Stop rosiglitazone and then start sitagliptin 100mg od, saxagliptin 5mg od or vildagliptin 50mg bd*
5=	GLP-1 mimetic (if not already on GLP-1 mimetic)	Negligible risk of hypos (if not used with SU). Some weight loss effects. Possible nausea & vomiting. Small pancreatitis risk. No cardiovascular safety evidence	May be suitable for some patients in whom weight loss may be particularly desirable (in line with NICE CG87 guidance) *Stop rosiglitazone and start exenatide 5µg bd. Titrate to 10µg bd. Alternatively liraglutide 0.6mg od titrated to 1.2mg could also be used. Consider delayed start by 4 weeks if patient is on SUs*
5=	Insulin (if not already on insulin)	Established and effective drug. Risk of hypoglycaemia. Risk of weight gain	May be suitable for some patients in whom HbA_{1c} is particularly high and/or who are on maximum or near maximum oral hypoglycaemic therapy *Stop rosiglitazone and then start insulin (choice is according to patient's individual needs)*

offered medications for which there are no safety data in pregnancy (such as incretin-based therapies or pioglitazone) unless they are using effective contraception. Also, all such women should be given appropriate pre-conception counselling.
• The local diabetes specialist team should be contacted for advice if needed.
• Prior evidence of heart failure or impairment of left ventricular function remains a contraindication for the use of these medications and this should be rigidly adhered to. Osteoporosis and previous fracture may also be considered a relative contraindication to a TZD in post-menopausal females.

ABCD will keep this advice under review as new information becomes available.

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Dr Niru Goenka has given lectures or attended meetings sponsored by MSD, Eli Lilly, Novo Nordisk and Bristol-Myers Squibb. Any honoraria from these meetings are paid either to the departmental diabetes education and research trust fund, or to other registered charities.

Dr Aled Roberts has received educational sponsorship and/or honoraria for lectures from Astra Zeneca, Novo Nordisk and MSD.

Dr Susannah Rowles has previously received speaker's fees from a number of pharmaceutical companies including Eli Lilly, GlaxoSmithKline, Sanofi-Aventis and Takeda.

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Table 2. Switching from rosiglitazone to pioglitazone

Current rosiglitazone dose	HbA_{1c}	Suggested initial dose of pioglitazone
4mg daily	≤7.5% (58mmol/mol)	15mg
4mg daily	>7.5% (58mmol/mol)	30mg
8mg daily	≤7.5% (58mmol/mol)	30mg
8mg daily	>7.5% (58mmol/mol)	45mg
If on Avandamet (rosiglitazone/metformin fixed dose combination) then individualised therapy as appropriate, or consider pioglitazone/metformin fixed dose combination if appropriate. The licensed starting doses of pioglitazone are 15mg and 30mg		
Algorithm based on advice from Takeda (manufacturer of pioglitazone) and on a review by Derosa, 2010.[12]		

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