



Pioglitazone Replacement Options

The European Medicines Agency has made the decision to continue the licence for pioglitazone after reviewing the long term safety data on this agent. While it was found that the reports of an increased risk of bladder cancer in pioglitazone users were likely to be a true effect, the risk is thought to be small. Setting this against the potential harm in stopping treatment in those who were responding well, the overall decision was to continue the licence. Nevertheless, the recommendation is to stop treatment in those at risk of or with existing bladder cancer.

The aim of this guidance is to consider alternative treatments for patients in whom it is decided to discontinue pioglitazone.

Pioglitazone, a thiazolidinedione, is a member of a group of pharmaceutical agents which act as insulin sensitisers. This effect is achieved by binding to an intranuclear receptor which upregulates certain key enzymes in glucose and fat metabolism. The importance of this mechanism of action is that withdrawal of pioglitazone treatment in any individual may not have any rapid consequences as the onset and offset of treatment effect is in the order of 6-12 weeks.

Glycaemic response to pioglitazone was somewhat idiosyncratic. Some individuals achieved significant improvements in glycaemic control with this treatment whereas others saw little change. It is, therefore, worth examining the records of any pioglitazone treated individual to assess their historic response to the treatment. This may help to predict the effect of withdrawal.

In those patients where pioglitazone appeared to be particularly effective, there is likely to be a progressive worsening of glycaemic control in the months after withdrawal and with an associated need to change to or introduce other therapies. Even in those where pioglitazone appeared less effective, there might be some deterioration in control after withdrawal.

The first option will be to consider the glycaemic control in that individual patient and decide if escalation of therapy is appropriate. There may be scope to increase the doses of concurrent hypoglycaemic agents to avoid the need to add other treatments.

Where up-titration of the doses of other medication is not possible, the fall back position will be to consider insulin treatment. In many cases, pioglitazone was used to delay the point where

insulin was required, and withdrawal may simply hasten the natural progression to escalate to insulin treatment.

There is likely to be a significant minority of individuals where the use of insulin is less desirable. This is likely to be where there is coexistent obesity, or where use of insulin would have implications for the individual's occupation. In those where insulin is not thought an ideal option, the use of incretin based treatments can be considered.

The DPP-IV inhibitors ('gliptins') have the advantage of oral administration, but have a mild blood glucose lowering effect (HbA_{1c} lowering of 0.5-1%). They may, however, be considered where the individual is not too far from their glycaemic target. In individuals where there is renal impairment, saxagliptin would be the agent of choice, as it has safety data in renal impairment.

Where an individual is significantly over their ideal weight, GLP-1 analogues can be considered. The current choices are exenatide (Byetta or its longer acting derivative) or liraglutide (Victoza). Like insulin, these are injectable treatments, and this facet needs to be discussed with patients before proceeding. It is difficult to predict who will respond to these agents. However, their weight reducing action is fairly consistent. Even if used as a prelude to insulin conversion, the weight loss associated with GLP-1 analogues is useful. Their use can, however, be limited by gastrointestinal side effects. It is important that patients understand that an important part of the effect of these medications is achieved by reduced appetite. Nausea is quite common at start of therapy but may reduce with time.

As a general consideration, it should be remembered that the long term side effects of the thiozolidinediones only became apparent with additional post licensing usage. In recommending the newer agents, it should be remembered that they have considerably less safety data behind them than the more established treatments such as metformin, sulphonylureas and insulin.

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