

The purpose of this factsheet is to emphasise the importance of appropriate prescribing of metformin in type 2 diabetes. As we know, in the UKPDS, significant improvements in macrovascular outcomes leading to fewer deaths were reported for overweight patients receiving metformin therapy for a median period of 10 years. The reduction in morbidity and mortality was much greater than that reported for patients treated with sulphonylureas and insulin despite there being no overall difference in glycaemic control. This emphasises the need to optimise therapy with metformin, so that these benefits can be more widely realised.

The Bottom Line

Metformin is the first-choice hypoglycaemic drug in type 2 diabetes, with a sulphonylurea as an alternative in certain circumstances. NICE states that if blood glucose control is inadequate on monotherapy (HbA1c above 6.5% [48mmol/mol] **or other higher agreed level**); dual therapy with metformin and a sulphonylurea is the preferred second-line therapy.

Initiating Metformin

- **Metformin should routinely be initiated at a dose of 500mg with breakfast for at least 2 weeks, then 500mg with breakfast and evening meal for at least 2 weeks, then 500mg with breakfast lunch and evening meal.**

The benefits observed in the UKPDS were achieved at a relatively high dose of metformin. Whilst more than half of the patients in the UKPDS received a daily dosage of 2550 mg/day, more than three quarters of patients received at least 1700 mg/day.

Managing Side Effects

- **Slow and steady dose titration over several weeks will result in a good tolerance to the drug and minimise the risk of gastrointestinal adverse effects.**

The majority of adverse effects associated with metformin are gastrointestinal, and usually appear soon after initiation. They can lead to discontinuation of therapy in up to 5% of patients. These adverse effects are usually transient however, and tend to subside over several months of continued therapy.

- **The maximum daily dosage of metformin is 3 g (in divided doses), although in practice, daily dosages above 2 g are rarely exceeded.**

Evidence suggests that increasing the metformin dose beyond 1500–2000 mg/day does not markedly increase the risk of gastrointestinal side effects or lactic acidosis, and fear of these side-effects should not prevent the achievement of optimal dosage levels in patients with type 2 diabetes. It may not be practical however to use the full dose range of metformin particularly if this is unlikely to achieve the glycaemic target. In the latter situation, the dosage should revert to the lowest dose to achieve the maximum effect and consideration given to combination therapy

- **Very weak evidence supports changing from standard-release metformin to modified-release metformin if gastrointestinal adverse effects prevent an individual continuing standard-release therapy.**

However, it may also be considered appropriate to consider the use of metformin MR if the alternative would be to consider the addition of other more expensive options.

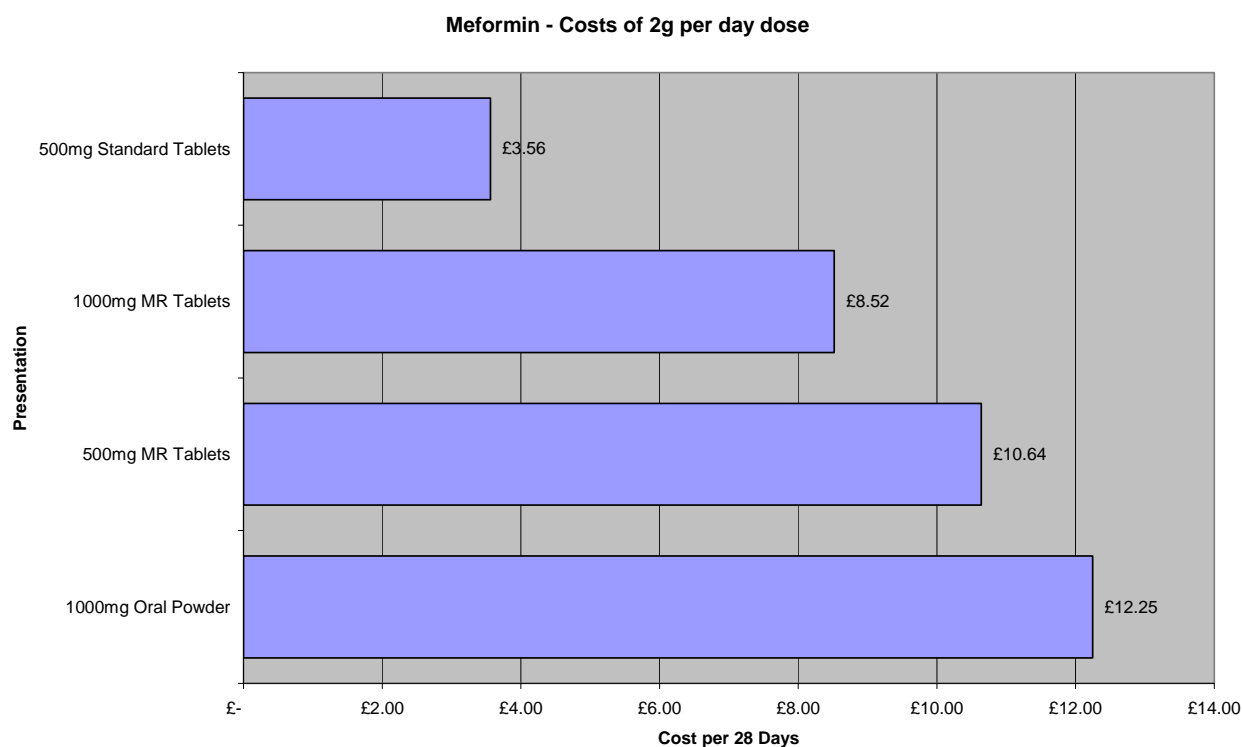
Renal Impairment

Metformin should be used with caution in renal impairment due to an increased risk of lactic acidosis. Although this complication is rare (0.3% of patients prescribed metformin per annum), NICE recommends that metformin prescribing should be reviewed if the eGFR is less than 45 mins/minute/1.73m² and to avoid altogether if the eGFR is less than 30 mins/minute/1.73m². Patients with acute kidney injury, and/or who are dehydrated are likely to experience a sudden deterioration in renal function. In these cases metformin may also need to be withdrawn or discontinued. When renal function improves, it may be appropriate to reinstate the metformin and monitor closely.

Patients with swallowing difficulties

There is an oral powder version of metformin, currently available as 500mg or 1g sachets. The contents of the sachet are mixed with 150mls of water and swallowed immediately. This preparation is significantly less expensive than metformin 500mg/5ml oral solution. A 28 day prescription of the sachets at 2g per day will cost £12.25 compared to £296 for the oral solution!

Metformin Preparation Cost Comparison



- **Metformin 500mg/5ml oral solution: £296 for 28 days**