



SUMMARY SHEET FOR

Repaglinide

(NovoNorm[®])

For the treatment of type 2 diabetes mellitus

Licensed indication

‘Repaglinide is indicated in patients with type 2 diabetes (non insulin-dependent diabetes mellitus [NIDDM]) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients who are not satisfactorily controlled on metformin alone.’¹

Background information

Diabetes mellitus is a common chronic disease, which is recognised world-wide as a major public health problem. It is associated with markedly increased morbidity and mortality. The majority of people in the UK with diabetes mellitus (~80%) have type 2 diabetes.² The primary defects in type 2 diabetes are reduced insulin secretion and insulin resistance.

Current treatment options

The key treatment goals in type 2 diabetes are the relief of acute symptoms and the prevention of long-term complications, whilst avoiding hypoglycaemia.

Dietary and lifestyle modifications form the mainstays of therapy for type 2 diabetes, but 50 to 70% of patients will also require an oral antidiabetic agent. Drug treatments currently available include the sulphonylureas, metformin, insulin secretagogues (nateglinide and repaglinide), acarbose, thiazolidinediones (rosiglitazone, pioglitazone), and insulin.

The United Kingdom Prospective Diabetes Study (UKPDS) established that tightly controlled blood glucose concentrations in patients with type 2 diabetes significantly reduces the risk of microvascular complications.³ The UKPDS also showed that metformin was associated with reduced risk of macrovascular complications.⁴ Metformin should be considered as the first treatment option for patients with type 2 diabetes.⁵

Repaglinide is rapidly acting and designed to target post-prandial hyperglycaemia. It stimulates insulin secretion when needed (i.e. at meal times) with return to basal insulin levels between meals. Like the sulphonylureas, its effect is dependent upon functioning β -cells in the pancreas.

Dosage and administration

The recommended starting dose of repaglinide is 0.5mg taken before main meals (or 1mg in patients transferred from another oral antidiabetic agent). The recommended maximum single dose is 4mg (maximum daily dose 16mg).¹

Clinical efficacy

The efficacy of repaglinide as monotherapy in type 2 diabetes has been evaluated primarily in placebo-controlled and sulphonylurea-controlled studies. One study assessed combined use with metformin. In these studies, the outcomes evaluated were predominantly changes in glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) levels.

Placebo-controlled studies

Four fully published studies compared 10–24 weeks repaglinide treatment (taken two or three times a day) with placebo in Type 2 diabetic patients (n = 99, 361, 408, 25).^{6–9} In these studies, HbA_{1c} and FPG levels fell from baseline with repaglinide (HbA_{1c} by –0.5% to –2.1% and FPG by –1.8mmol/l to –3.9mmol/l) compared with placebo (+1.4% to –0.15% and +1.1mmol/l to –0.4mmol/l). Post-prandial glucose levels, assessed in two studies, showed a similar trend (–3.1 to –6.2mmol/l repaglinide, vs. +0.2 to +2.3mmol/l placebo).^{6,9}

Comparative studies with sulphonylureas

Four fully published studies have compared repaglinide and glibenclamide treatment. One 14-week study¹⁰ and two 12-month studies^{11,12} assessed fixed dosing of repaglinide, and one 10-week study assessed flexible dosing.¹³

In the 14-week study (n=195), conducted in patients previously treated with sulphonylureas, HbA_{1c} and FPG levels fell in both treatment groups, with no significant difference between groups at study end.¹⁰ In both 1-year studies (n = 425, 576), glycaemic control worsened with both repaglinide and glibenclamide to a similar extent, with HbA_{1c} and FPG levels increasing from baseline.^{11,12}

In the 10-week study (n = 235), on days of two meals (4 weeks during Ramadan) patients omitted their lunchtime dose of repaglinide. The control group continued on glibenclamide once or twice daily. Post-Ramadan there were no significant changes in HbA_{1c} in either group.¹³

Two one-year studies have compared repaglinide to the sulphonylureas glipizide¹⁴ and glimepiride.¹⁵

After one year, HbA_{1c} and FPG levels had increased in both the glimepiride and repaglinide groups, with no significant differences between the groups.¹⁵ In patients who had previously been exposed to oral antidiabetic drugs, repaglinide showed improved efficacy over glipizide, with significantly smaller increases in HbA_{1c} and FPG ($p < 0.05$).¹⁴

Studies in combination with metformin

A small ($n=83$) 4-to-5-month study evaluated repaglinide and metformin combination therapy in patients not optimally controlled on metformin alone.¹⁶ In this study, HbA_{1c} and FPG levels fell significantly with combination therapy, both from baseline ($p < 0.002$) and compared with either drug alone ($p < 0.05$). By the end of the study, nearly 60% of patients receiving combination therapy had optimal glycaemic control (HbA_{1c} $< 7.1\%$), compared with 20% in both monotherapy groups.

Repaglinide has been compared with nateglinide in combination with metformin in one open-label study ($n=192$).¹⁷ After 16 weeks there were significantly greater reductions in HbA_{1c} and FPG with the repaglinide + metformin combination (-1.28% and -2.2mmol/l) than with the nateglinide + metformin combination (-0.67% and -1.2mmol/l).¹⁷

Adverse effects

The most common adverse events across the studies were those related to hypoglycaemia (mostly mild to moderate events). The frequency of hypoglycaemia with repaglinide and glibenclamide were similar.

Other adverse effects reported rarely were abdominal pain and nausea, and allergic skin reactions.¹ See the Summary of Product Characteristics (SPC) for additional information on very rare adverse events.¹

Costs

At current prices, one year's treatment costs:

- £148 with repaglinide 6mg a day
- £195 with nateglinide 360mg a day
- £67 with gliclazide 160mg a day
- £31 with glibenclamide 10mg a day.

Summary

Repaglinide is an insulin secretagogue licensed for use as monotherapy and in combination with metformin in patients with type 2 diabetes.

In clinical trials of repaglinide monotherapy, glycaemic control was improved compared with placebo, and was generally similar to that found with sulphonylureas. In combination with metformin, improved glycaemic control was seen compared with either drug alone. The most common adverse events across the studies were those related to hypoglycaemia. Most were mild to moderate events.

The rapid onset, short duration of action and flexible dosing schedule of repaglinide may offer some benefits to some patients with type 2 diabetes.

References

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