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Repaglinide (NovoNorm) in the management of Type 2 diabetes

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7. recognise the quality and maximise the work satisfaction of its staff and their contribution to the School.

Professor Ron Akehurst, Dean of ScHARR

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Background

Diabetes is a common chronic disorder. Approximately 2% of the UK adult population have been diagnosed as having diabetes. Community prevalence studies suggest a similar number of undiagnosed cases[1]. The prevalence varies a great deal across age groups and by ethnic origin. The South Asian and Afro-Caribbean communities have much higher prevalence. The prevalence appears to increase with age in all communities.

There are two main types of diabetes, insulin dependent diabetes mellitus (IDDM), often called Type 1 diabetes; and Non-insulin dependent diabetes (NIDDM), known as Type 2. Type 1 diabetes accounts for approximately 10% of all diabetes cases. Table 1 is based on Williams[2] and estimates the prevalence of Type II diabetes by age group, in a representative health authority with a population of 500,000. This analysis indicates that over 2 million people in the UK have Type 2 diabetes.

Table 1: Estimate of the prevalence of Type 2 (Non-insulin Dependent Diabetes) in a Health Authority Population (n=500,000)

Age	Population	Number of Cases	Lower 95% Confidence Interval	Upper 95% Confidence Interval
0-9	62800	3	0	25
10-19	68200	0	0	24
20-29	80200	88	48	140
30-39	68600	103	65	144
40-49	61800	254	201	319
50-59	53200	481	399	579
60-69	50400	791	689	905
70-79	36400	1021	902	1152
80+	18400	474	386	582

Diabetes is characterised by the range and potential severity of its comorbidities. People with diabetes face increased risk of cardiovascular disease, renal failure, peripheral vascular disease, peripheral neuropathy and retinopathy. The recently published UKPDS studies have shown that both good blood glucose control (HbA1 <7%) and blood pressure control (systolic $\geq$160 and/or diastolic > 90 mmHg) are highly effective in limiting the risk of these comorbidities[3, 4, 5]. Consistent with this high risk of comorbidities, is the large expenditure by the National Health Service on the care

of people with diabetes. Williams reports a minimum estimate of 4% of total health care expenditure[2].

Current Treatment of Type II Diabetes

Type II diabetes is managed initially through the restriction of energy and carbohydrate energy and physical activity. When a patient has been shown to respond inadequately to these measures, oral antidiabetics can be prescribed.

The British National Formulary (BNF) describes three categories of oral antidiabetic: Sulphonylureas, Biguanides and 'Other antidiabetics'[6].
Currently there are eight sulphonylureas, (Chlorpropamide, Glibenclamide, Gliclazide, Glimepiride, Glipizide, Gligquidone, Tolazamide and Tolbutamide), one biguanide (metformin) and two other antidiabetics (glucobay and gluarem), listed in the BNF. There are generic versions of some of the sulphonylureas and of the biguanide.

Sulphonylureas act by augmenting the individual's own insulin secretion. By implication they are effective only when the individual retains some pancreatic function.

Chlorpropamide and Glibenclamide are long acting sulphonylureas and as such may carry an increased risk of hypoglycaemia compared to the shorter acting agents such as tolbutamide and gliclazide [6]. On this basis, these sulphonylureas are not recommended for elderly patients, due to their higher risk of hypoglycaemia.

Sulphonylureas are generally contra-indicated for patients with impaired hepatic or renal function. Obese patients may be better treated with metformin due to the weight gain that is often associated with this therapy. They are completely contraindicated in the presence of ketoacidosis. Caution in pregnancy is advised, and pregnancy is a contraindication for Glimepiride, where animal studies have demonstrated toxicity. Breastfeeding is a contraindication for all the sulphonylureas.

CONTENTS

In addition to hypoglycaemia, the side effects associated with sulphonylureas are mostly gastrointestinal discomfort and headache. These tend to be mild and infrequent.

Metformin, the only available biguanide has a different mode of action from the sulphonylureas. It is used in the treatment of non-insulin dependent diabetes when strict diet and sulphonylurea treatment has failed to produce adequate blood sugar control. It may be used as a monotherapy or in combination with a sulphonylurea.

The contraindications for metformin are greater than for the sulphonylureas including, predisposition to lactic acidosis, heart failure, severe infection or trauma, dehydration, alcohol dependence, pregnancy and breastfeeding. The side effects are more numerous and generally more severe in nature than for the sulphonylureas; including anorexia, nausea, vomiting, diarrhoea, lactic acidosis, and decreased vitamin B12 absorption.

With the current range of therapies, some patient groups are not well catered for, notably, the elderly.

Table 2 gives information on dosage and costs per day for all the antidiabetic drugs currently included in the British National Formulary (BNF).

Table 2: Dosage and cost per day for current anti-diabetic therapies

Drug	Min Dose mg	Max Dose mg	Cost min	Tabs min	mg per tab min	Cost max	Tabs max	mg per tab max	Daily cost per min dose	Daily cost per max dose
Sulphonylureas										
Chlorpropamide	250	500	18	20	100	27	20	250	£2.25	£2.70
Glibenclamide	5	15	30	20	2.5	35	20	5	£3.00	£5.25
Daonil	5	15	2.63	28	5				£0.09	
Semi-Daonil	5	15	1.58	28	2.5				£0.11	
Euglucon	5	15	1.58	28	2.5	2.63	20	5	£0.11	£0.39
Glicazide	80	320	3.2	28	80	6.75	60	80	£0.11	£0.45
Diamicron	80	320	7	60	80				£0.12	
Glimepiride/Amaryl	1	4	4.9	30	1	16.1	30	4	£0.16	£0.54
Glipizide	5	40	4.08	56	5				£0.07	
Glibenese	5	40	3.63	56	5				£0.06	
Minodiab	2.5	40	3.31	60	2.5	3.54	60	5	£0.06	£0.47
Gliquidone/Glurenorm	15	180	17.54	100	60				£0.04	
Tolazamide/tolanase	100	1000	5.65	100	100	12.29	100	250	£0.06	£0.49
Tolbutamide	500	2000	0.4	20	500				£0.02	
Rastinon	500	2000	3.33	100	500				£0.03	
Biguanides										
Metformin	1500	3000	0.37	20	500	62	20	850	£0.06	£10.94
Glucophage	1500	3000	2	84	500	2.22	56	850	£0.07	£0.14
Other antidiabetics:										
Glucobay	50	600	14.1	90	50	17.7	90	100	£0.16	£1.18
Guarem	15000	15000	8.7	50	5000	15.67	100	5000	£0.52	£0.47
Repaglinide	**0.5**	**16**	**17.57**	**90**	**0.5**	**20.10**	**90**	**2**	**£0.20**	**£1.79**

Information obtained from BNF and NovoNorm Product Summary
Min = Minimum; Max = Maximum; Tabs = Tablets; mg=milligrams.

Repaglinide

Repaglinide is a new antidiabetic, belonging to a new class of antidiabetic, the carbamoylbenzoic acid derivatives. Although structurally different from sulphonylureas, Repaglinide also acts through the stimulation of insulin secretion.[7] The process of insulin secretion is partially distinct from that of the sulphonylureas. [8]

Repaglinide has been approved as a monotherapy and as combination therapy with metformin where metformin monotherapy does not produce satisfactory blood glucose control[9].

Repaglinide is the first of a new class of antidiabetic agent, called 'prandial glucose regulators'. They have a very rapid mode of action combined with a short duration of activity. The effect of this is that they can be used to stimulate the secretion of insulin just prior to eating, without carrying a risk of hypoglycaemia between meals and/or overnight. [7] This may be of particular value for patients at increased risk of hypoglycaemia such as the elderly. Both the UKPDS and the DCCT study have highlighted the importance of managing glycaemic exposure in reducing the risk of morbidity and mortality in NIDDM[3 10].

Evidence on Safety and Efficacy

The UKPDS established the importance of blood glucose regulation in reducing the risk of mortality and morbidity in NIDDM[3]. Currently there are eight papers in peer reviewed journals reporting randomised controlled trials (RCT) of Repaglinide. These trials are described briefly below.

1. **An open label, randomised group comparison study of repaglinide versus glibenclamide in 44 patients with NIDDM already treated with sulphonylureas**[11]. Glibenclamide had a greater effect on fasting blood glucose and repaglinide significantly lowered postprandial blood glucose. Both treatments reduced total cholesterol. No abnormal findings attributable to repaglinide were observed in clinical

and laboratory examination and no hypoglycaemic symptoms caused by repaglinide were observed.

2. **A randomised placebo controlled trial of Repaglinide**[12]. Ninety-nine patients were randomly allocated to either placebo or Repaglinide on a 1:2 ratio. After a two week washout period and 6 weeks dose adjustment, patients were followed up for 12 weeks on their maintenance dose. This study found mean HBA1c reduced significantly between baseline and last visit for patients on Repaglinide, whilst it increased for patients on placebo. Repaglinide was safe and efficacious and shown to have a 'potent glucose lowering effect in the postprandial period'. There were more cardiovascular adverse events in the Repaglinide arm. Further investigation showed that these were generally in patients with established histories and unlikely to be related to the study medication.

3. **A multi-centre double blind randomised controlled trial of Repaglinide and glyburide**[13]. Four hundred and twenty four patients were randomly allocated on a 2:1 ratio between Repaglinide and glyburide. After a six to eight-week dose titration period, patients were followed up for one year. There were no statistically significant differences in the time profile in Hba1c control nor in the incidence of adverse events. The study concluded that 'Repaglinide is a safe and efficacious oral blood glucose lowering agent, with potency similar to that of glyburide'.

4. **A randomised double blind trial of Repaglinide addition to metformin monotherapy**[14]. Eighty three patients with poor control on metformin alone were recruited and randomised to metformin monotherapy (n=27), metformin (n=27) and Repaglinide , or Repaglinide alone (n=29). A four to eight-week titration period was used to establish the optimum dose of Repaglinide where relevant. Metformin was fixed at pre-study dosage. Patients were followed-up for a three-month maintenance period. Hba1c decreased significantly in the metformin plus Repaglinide group, over the duration of the study. The outcomes were in monotherapy groups were comparable at baseline and last visit. Symptomatic hypoglycaemia was reported most frequently in the combination therapy group and not at all in the metformin treated group. The study concluded that combined therapy produced better glycaemic control

than metformin alone and that Repaglinide monotherapy was comparable to metformin monotherapy.

5. **A prospective 1 year multi-centre double blind randomised, parallel group trial of glyburide and Repaglinide in patients with type 2 diabetes**[15]. Five hundred and seventy six patients were randomised to receive Repaglinide or glyburide monotherapy. An eight-week titration period was used to achieve a fasting blood glucose target. The titrated dose was then maintained for 12 months. Repaglinide provided glycaemic control at least as effective as glyburide. Overall, safety and changes in lipid profile and weight were similar for both groups. Repaglinide at doses of 0.5 to 4 mg, administered pre-prandially, 3 times a day, was well tolerated, effective and safe over the 12 months of follow-up.

6. **A double blind randomised comparison of meal–related glycaemic control by repaglinide and glyburide in well-controlled type 2 diabetes patients**[16]. Of 83 patients randomised, and entered in to the titration phase of the study, 43 were entered into a 3 day study period in which half of the patients received 2 meals on the first day and 3 meals and the second and third day, the other half receiving 3 meals on the first day and two meals on the second and third days. All hypoglycaemic events observed in this study were in glyburide treated patients on days when they received only two meals i.e. lunch was skipped. The study concluded that the management of people with Type 2 diabetes who miss or delay a meal is superior with repaglinide compared to glyburide.

7. **A comparison of repaglinide and glibenclamide in the treatment of type 2 diabetic patients previously treated with sulphonylureas** [17]. One hundred and ninety five people who fitted the study criteria were randomised to receive either repaglinide or glienclamide, for 14 weeks, in order to compare the efficacy and safety within this patient group. The safety profile was similar with a non-significant increase in mild and moderate hypoglycaemic events in the repaglinide group compared to the glibenclamide group. The two hour postprandial blood glucose level was lower in the repaglinide group, but this difference was not statistically significantly, ($p=0.068$). There was no difference in the mean blood glucose levels nor the mean blood glucose level relative to fasting blood glucose. The therapeutic

advantage of repaglinide reported in sulphonylurea naïve patients was not reproduced in this study[18].

8. **Flexible prandial glucose regulation with repaglinide in patients with Type 2 diabetes**[19]. In this open label study twenty five patients were randomised across three meal regimes, for 20 days (3 meals a day; 4,3,2,3 meal days over 5 four day cycles; and 2,3,4,3 meals a day over 5 four day cycles). The objective was to assess the efficacy of repaglinide in maintaining glycaemic control when meals are missed. There was no significant difference in the serum fructosamine between the groups. The maximum blood glucose concentration was lower for patients on the 2 meal days, than patients on the fixed or 4 meal days. This difference approached statistical significance. There was no significant difference in the incidence of adverse events between the groups. No hypoglycaemic events were observed during the study.

In addition to the published trials, six studies have been presented at scientific conferences. Two further studies, described as data on file, have been referred to in a recent review by the Midland Therapeutic Review and Advisory Committee (MTRAC). [20] Four strong themes can been seen in the work to date:

1. Improved post prandial blood glucose levels
2. Comparable or superior efficacy of Repaglinide and the sulphonylureas;
3. Efficacy of Repaglinide when used as a 'flexible pre-prandial' therapy; and
4. Longer term safety of Repaglinide therapy.

The MTRAC commentary highlighted the issue of observed differences in the incidence of cardiovascular adverse events between the Repaglinide and glyburide/glibenclamide. Their conclusion stated that 'due to concerns regarding safety, general practitioners are advised not to prescribe this drug.' [20] By contrast the Committee for Proprietary Medicinal Products concluded that "... after statistical/epidemiological assessment of the data considering multiplicity testing and analysis of missing values and also taking into account the pooled data with all sulfonylureas in the comparative trials and the background frequency in patients with

Type 2 diabetes it was concluded that Repaglinide did not pose any increased risk of cardiovascular events'. [21]

Following the MTRAC review, Campbell, Professor of Medical Statistics at the University of Sheffield revisited the issue [22]

The crude absolute risk for all cardiovascular adverse events was higher for Repaglinide than glibenclamide in each of the three comparative trials. These differences were not observed in the comparative trials between Repaglinide and gliclazide.

By analysing available ECG data for baseline and final follow-up, Campbell showed an apparent excess in the number of patients whose baseline ECGs were normal, but final ECGs were abnormal, for patients on Repaglinide compared with glibenclamide. However, the difference was not statistically significant.

Campbell concludes:

'That there is no evidence that Repaglinide causes an increase in mortality or non-serious cardiovascular side effects compared with any other drugs."

Table 2 gives the cost per day of treatment for the minimum and maximum dosage, for all the antidiabetics currently listed in the BNF, and for Repaglinide. The costs have been calculated with the assumption that the minimum dosage will use the smaller prescribing units i.e. tablets per pack, and the maximum dosage will use the larger prescribing units. It is clear that prescribing Repaglinide represents a significant increase in the treatment cost per patient.

There are, potentially, two reasons for prescribing Repaglinide to a patient rather than their current therapy:

1. The health gain associated with Repaglinide compared to current therapy is sufficient to justify the additional cost; and
2. The adverse events avoided due to the use of Repaglinide rather than current therapy, are sufficient for Repaglinide to have a neutral or cost saving impact on the total cost of care for patient.

Fox suggests that approximately 25% of people currently on Sulphonylureas and 13% of patients on other antidiabetic therapies, would be candidates for Repaglinide therapy. These would be (a) newly diagnosed cases, who are deemed to be at significant risk hypoglycaemia, (b) patients whom current therapy is failing to produce adequate glycaemic control, and (c) patients who are actively involved in the management of their condition. [23]

Adapting Fox's calculations for a population of a typical health authority (500,000), there should be 833 patients who might be prescribed Repaglinide in the first instance.

Brown, suggests 6mg per day as an average dose for Repaglinide. Assuming this proves to be correct, the cost per person per day on the 2mg tablets, would be £0.68. The annual cost per person per year would be £248 and the annual cost for the health authority would be £207,000.

Whilst there will be some cost offset from patients switched from other sulphonylureas or metformin, these are unlikely to be greater than 30%, given the minimum and maximum daily cost data presented in Table 2. On this basis the additional cost per patient is £174 per year. This equates to an additional £145,000 per year for the average health authority.

This level of additional expenditure is unlikely to be maintainable by most health authorities in the United Kingdom. It will be necessary to identify those patients who will receive the greatest benefit from switching to Repaglinide, in order to maximise the health benefit from whatever level of additional expenditure is affordable.

Within the NHS, prioritisation decisions are increasingly informed by assessments of the cost per quality adjusted life year gained, from a new therapy over current treatment. As a rule of thumb, therapies which exceed £10,000 per quality adjusted life year gained are unlikely to be recommended for purchasing. Therapies that have a cost per quality adjusted life year gained less than £3000 are highly recommended.[24]

To demonstrate a cost per quality adjusted life year gained at the £10,000 threshold, Repaglinide needs to identify patients in whom the switch to Repaglinide improves their quality of life by at least 3.2 points (on scale of 0 to 100, where 0 equals dead and 100 equals perfect health). To be highly recommended for purchasing, a quality of life improvement around 10.8 points, must be demonstrated. Using the EQ-5D instrument, repaglinide therapy would have to move the patient from level 2, to level 1, on at least one of the five dimensions. (See Appendix).[25]

These exploratory analyses have assumed that there is no mortality benefit for Repaglinide over current therapies, and that there are no realisable cost savings available to the service from switching patients to Repaglinide. The UKPDS results, suggest that mortality and morbidity benefits are possible in patients for whom current therapies do not produce adequate blood glucose control [3 4 5]

Discussion

Repaglinide is novel oral hypoglycaemic agent, with a different mode of action to the current antidiabetic therapies. To date, trials involving slightly over 1500 patients, have been reported in peer reviewed journals. These trials consistently report equivalent efficacy and safety to the current range of therapies, and superior efficacy in some specific patient groups.

The characteristics of the drug, specifically the rapid absorption and elimination, suggest that there may be patient subgroups in which Repaglinide will offer significant health/quality of life benefits; specifically patients at high risk of post-prandial hyperglycaemia and those with irregular eating patterns. Research to quantify and value these quality of life benefits would be very useful to health policy decision-makers.

Given that the NHS is unlikely to be able to afford Repaglinide for all patients who might benefit, prioritisation will be required. Cost effectiveness is one basis on which this could be done. Therefore, in addition to the additional clinical data described above, data on the quality of life improvement available from Repaglinide therapy in the patient sub-groups identified above, will be essential, for a full consideration of its role in the management of type 2 diabetes in the NHS.

Appendix

EUROQOL© HEALTH QUESTIONNAIRE

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

Please tick one

1. Mobility

I have no problems in walking about ○

I have some problems in walking about ○

I am confined to bed ○

2. Self-care

I have no problems with self-care ○

I have some problems washing or dressing myself ○

I am unable to wash or dress myself ○

3. Usual Activities

I have no problems with performing my usual activities ○
(e.g. work, study, housework, family or leisure activities)

I have some problems with performing my usual activities ○

I am unable to perform my usual activities ○

4. Pain/Discomfort

I have no pain or discomfort ○

I have moderate pain or discomfort ○

I have extreme pain or discomfort ○

5. Anxiety/Depression

I am not anxious or depressed ○

I am moderately anxious or depressed ○

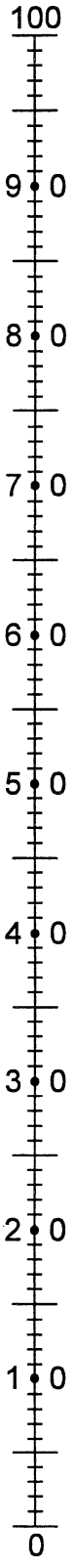
I am extremely anxious or depressed ○

6. To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

   We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today

Best imaginable health state



Worst imaginable health state

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