

# The Clinical and Cost-effectiveness of Pioglitazone and Rosiglitazone in the Treatment of type 2 Diabetes

**VERSION WITH CONFIDENTIAL INFORMATION EXCLUDED**

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## **ABOUT THE TRENT INSTITUTE**

Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield, with support from NHS Executive Trent. Members of staff in the Sheffield Unit, based in the School of Health and Related Research (SchARR), have been engaged in reviewing the effectiveness and cost-effectiveness of health care interventions in support of the National Institute for Clinical Excellence.

In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are The Wessex Institute for Health Research and Development, Southampton University, The University of Birmingham Department of Public Health and Epidemiology, The Centre for Reviews and Dissemination, University of York.

### **Contributions of authors**

Carolyn Czoski-Murray and Johanna Cowan carried out the review of clinical effectiveness. Emma Warren, Jim Chilcott and Maria Psyllaki carried out the review of cost effectiveness. Catherine Beverley carried out the electronic searches.

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## EXECUTIVE SUMMARY

### Objectives

The aim of this review was to evaluate the use of pioglitazone and rosiglitazone, in terms of both clinical and cost effectiveness.

### Methods

A systematic review of the literature, involving a range of databases, was performed to identify all papers relating to the glitazones. Full details are described in the main report.

### Results

Total number of studies identified from these searches was 1272.

#### Number and Quality of studies

9 studies met the inclusion criteria.

#### Clinical effectiveness

The clinical evidence available showed that glitazones reduce HbA1c by approximately 1%, and are more effective at higher doses than at lower doses. There is significant weight gain associated with glitazone treatment. No data were available on the long-term effects of glitazone use. No prospective randomised controlled trials were found comparing pioglitazone to rosiglitazone, but the available evidence showed that the two treatments had similar effects.

#### Health Economics

There are no published economic studies on either pioglitazone or rosiglitazone. An economic evaluation both glitazones has been provided by the associated sponsor. Given the lack of a published evidence base for the cost-effectiveness of the glitazones, the economic review concentrates on a review of the industry submissions. In spite of the stress in the NICE 'Guidance for Manufacturers and Sponsors' that sponsors provide transparent economic models with a full range of sensitivity analyses performed, neither GSK nor Takeda fulfilled this requirement. Even though this review is an up-date of the original glitazones review, all the economic evidence presented in the Takeda submission and the majority of the new evidence presented in the GSK submission is still marked 'Commercial in Confidence'.

The GSK industry submission concludes that rosiglitazone is cost-effective (in terms of cost per QALY) in all scenarios, whether combined with metformin or sulphonylurea.

**Table I: Cost effectiveness results reported in the GSK submission**

Treatment arm	Comparator	Cost per QALY	Cost per LYG
Rosi + SU (lean)	SU to insulin	Rosi dominates	Rosi dominates
Rosi + SU (overweight)	SU to insulin	Rosi dominates	Rosi dominates
Rosi + Met	Met to insulin	Rosi dominates	Rosi dominates
Rosi + Met	Met + SU	£9,972	£262,253
Rosi + Met	Met + SU to Rosi + Met	£11,857	£259,591

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## **Table II: Cost effectiveness results reported in the Takeda submission**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results of the sensitivity analyses suggest that the cost per QALY of rosiglitazone is most sensitive to two variables; dosage and a change in the treatment effect i.e. effect of rosiglitazone on beta-cell function and insulin sensitivity. ScHARR have performed some sensitivity analyses on the treatment effect to determine the effect on the cost-effectiveness. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

In the two scenarios where rosiglitazone is compared to metformin and sulphonylurea combination therapy, the cost-effectiveness of rosiglitazone switches from being cost-effective to being dominated by the comparator strategy.

This suggests that small changes in the effect of rosiglitazone on beta-cell function and insulin sensitivity induce large changes in the cost per QALY ratios. Therefore there is a high level of uncertainty associated with the treatment effect of rosiglitazone. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.* As seen in table 77, the cost per QALY ratio of rosiglitazone increases significantly if it is assumed that 100% of patients receive 8mg.

GSK did not perform any univariate or multivariate sensitivity analyses on the model. Furthermore, due to the complexity of the model it has not been possible within the rapid review timescales to do a full multivariate analysis. The univariate sensitivity analyses that have been performed indicate that there is a wide degree of uncertainty, for example ranging from a cost effectiveness under £20,000 per QALY to being dominated, in the key scenarios under consideration.

The cost per QALY ratios presented in the GSK model suggest that rosiglitazone therapy, combined with either metformin or sulphonylurea, is an economically attractive option. The current NICE guideline suggests that glitazone combination therapy should only be tried after metformin and sulphonylurea combination therapy has failed. However, the cost per QALY ratios presented in the GSK model suggest that it is potentially economically viable to use rosiglitazone combination therapy directly after failure of monotherapy with either metformin or sulphonylurea. However, since the baseline estimate of cost effectiveness is not robust to changes in the treatment effect and is reliant on the many assumptions included within the

metabolic and long term economic models caution should be used in interpreting this baseline favourable result.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## LIST OF ABBREVIATIONS

<b>AMI</b>	Acute myocardial infarction
<b>ATV</b>	Atorvastatin
<b>B1</b>	Blindness in one eye
<b>B2</b>	Blindness in both eyes
<b>BCF</b>	Beta cell function
<b>BDR</b>	Background diabetic retinopathy
<b>BMI</b>	Body mass index
<b>BP</b>	Blood pressure
<b>CHD</b>	Coronary heart disease
<b>CI</b>	Confidence interval
<b>CIGMA</b>	Continuous infusion of glucose with model assessment
<b>CPK</b>	Creatinine phosphokinase
<b>CVD</b>	Cardiovascular disease
<b>D&amp;E</b>	Diet & exercise
<b>DARTS</b>	Diabetes audit and research in Tayside Scotland
<b>DBP</b>	Diastolic blood pressure
<b>DCCT</b>	Diabetes control and complications trial
<b>DFU</b>	Diabetic foot ulceration
<b>DKA</b>	Diabetic ketoacidosis
<b>ECG</b>	Electrocardiograph
<b>ESRD</b>	End-stage renal disease
<b>FDA</b>	Food and drug administration
<b>FPG</b>	Fasting plasma glucose
<b>FPI</b>	Fasting plasma insulin
<b>GDM</b>	Gestational diabetes mellitus
<b>GP</b>	General practitioner
<b>GPR</b>	Gross proteinuria
<b>GSK</b>	GlaxoSmithKline
<b>HbA1c</b>	Glycated (glycosylated) haemoglobin
<b>HDL</b>	High density lipoprotein
<b>HOMA</b>	Homeostasis model assessment

<b>I</b>	Insulin
<b>ICER</b>	Incremental cost-effectiveness ratio
<b>IDDM</b>	Insulin-dependent diabetes mellitus
<b>IFG</b>	Impaired fasting glucose
<b>IGT</b>	Impaired glucose tolerance
<b>INS</b>	Insulin
<b>IS</b>	Insulin sensitivity
<b>LDL</b>	Low density lipoprotein
<b>LEA</b>	Low extremity amputation
<b>LS</b>	Least squares
<b>LYG</b>	Life year gained
<b>M</b>	Metformin
<b>MA</b>	Microalbuminuria
<b>Met</b>	Metformin
<b>MO</b>	Macular oedema
<b>N/A</b>	Not applicable
<b>NHANES3</b>	National health and nutrition examination survey
<b>NHS</b>	National health service
<b>NHS EED</b>	NHS Economic evaluation database
<b>NICE</b>	National institute for clinical excellence
<b>NIDDM</b>	Non-insulin-dependent diabetes mellitus
<b>OGTT</b>	Oral glucose tolerance test
<b>OHE HEED</b>	Office of health economics Health economic evaluation database
<b>P</b>	Pioglitazone
<b>PDR</b>	Proliferative diabetic retinopathy
<b>PG</b>	Plasma glucose
<b>PIO</b>	Pioglitazone
<b>PPAR<math>\gamma</math></b>	Peroxisome proliferator-activated receptor gamma
<b>PVD</b>	Peripheral vascular disease
<b>QALY</b>	Quality adjusted life year
<b>R</b>	Rosiglitazone
<b>REP</b>	Rochester epidemiology project, Minnesota

<b>ROSI</b>	Rosiglitazone
<b>RSG</b>	Rosiglitazone
<b>S</b>	Sulphonylurea
<b>SBP</b>	Systolic blood pressure
<b>SCI</b>	Science citation index
<b>SIGN</b>	Scottish intercollegiate guidelines network
<b>SKB</b>	SmithKlineBeecham
<b>SmPC</b>	Summary of product characteristics
<b>Sul</b>	Sulphonylurea
<b>T2DM</b>	Type II diabetes mellitus
<b>TC</b>	Total cholesterol
<b>TG</b>	Triglycerides
<b>TZD</b>	Thiazolidinediones
<b>UKPDS</b>	United Kingdom prospective diabetes study
<b>WESDR</b>	Wisconsin Epidemiologic Study of Diabetic Retinopathy
<b>WHO</b>	World health organisation
<b>WMD</b>	Weighted mean difference

## **1. AIM OF THE REVIEW**

The aim of this review is to evaluate the incremental clinical and cost effectiveness of pioglitazone and rosiglitazone for the treatment of type 2 diabetes.

Specific objectives are:

- To evaluate the relative clinical effectiveness, in terms of glycaemic control and the incidence of hypoglycaemic events.
- To estimate the relative clinical effectiveness in terms of prevention of the longer-term complication of diabetes mellitus.
- To estimate the relative effect on overall mortality and quality-of-life adjusted mortality.
- To estimate the incremental cost-effectiveness of the glitazones.
- To estimate the possible cost impact on the NHS in England and Wales.

## **2. BACKGROUND**

### **2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM**

#### **2.1.1 Definition of diabetes mellitus**

Diabetes mellitus is a group of chronic disorders characterised by elevated blood glucose levels (hyperglycaemia). This is a consequence of inadequate control of glucose in the blood by the pancreatic hormone insulin and/or abnormal resistance to insulin. A specialised definition is given below by World Health Organisation (WHO).

The WHO defines diabetes mellitus as “a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both”.<sup>1</sup>

Glucose is the principal energy source for cellular metabolism and efficient metabolism depends on an optimum blood glucose concentration. Insulin is secreted by  $\beta$  cells in the islets of Langerhans of the pancreas. Normally, the concentration of insulin in the blood increases in response to an elevation in blood glucose levels that occur naturally after eating. The action of insulin on a number of cells, including muscle and fat cells, results in absorption of glucose out of the blood, thus maintaining blood glucose levels within the normal range. Hyperglycaemia results from a total or partial lack of insulin available or ineffectual for this function. The potential consequences of hyperglycaemia are damage to many of the body's systems; in particular, the blood vessels and nerves. Loss of glycaemic control is associated with long-term complications and people with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.<sup>2</sup>

There are two main aetiological types of diabetes:

- Type 1 diabetes mellitus (previously termed insulin-dependent diabetes mellitus, IDDM) is a condition in which the pancreas makes little or no insulin because the islet  $\beta$  cells have been destroyed through an autoimmune mechanism. The insulin-dependent tissues are less able to take up glucose and therefore there is a build-up of glucose in the body.
- Type 2 diabetes mellitus (previously termed non-insulin dependent diabetes mellitus, NIDDM) is caused by two factors: the reduction in insulin production and the presence of insulin resistance in skeletal muscle and liver. Type 2 diabetes is a progressive disease in which insulin production declines as the disease progresses, resulting in increasing failure of glucose uptake into cells. In early stages of type 2 diabetes, the most significant pathology is lack of insulin secretion. Type 2 diabetes appears when insulin secretion from the pancreas falls below a level that can maintain normoglycemia. As the disease progresses, insulin resistance remains relatively stable and insulin production declines progressively.

In addition to type 1 and 2 diabetes, the WHO classification system includes a number of other aetiological types:

- Other specific types
- Genetic defects of islet  $\beta$  cells function

- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug or chemical-induced diabetes
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes associated with diabetes
- Gestational diabetes mellitus (GDM) (diagnosed during pregnancy)

Individuals with diabetes mellitus may be further subdivided according to treatment, as follows:

- Patients not requiring insulin.
- Patients who use insulin in order to control blood glucose levels.
- Patients who require insulin for survival.

The criteria for the diagnosis of diabetes in non-pregnant adults is (all values given for venous plasma):

- Symptoms of diabetes and a casual plasma glucose  $\geq 11.1$  mmol/l (200 mg/dl). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss.
- FPG (fasting plasma glucose)  $\geq 7.0$  mmol/l (126 mg/dl). During the test a sample of blood is obtained following a period of not eating or drinking (except water) for at least 8 hours.
- 2 hour PG  $\geq 11.1$  mmol/l (200 mg/dl) during an OGTT. During the test a fasting blood sugar is obtained initially. The person is then asked to drink a sugary beverage (75g anhydrous glucose dissolved in water). Blood glucose levels are then obtained every 30 minutes for the next 2 hours. A blood glucose level below 140 mg/dl at 2 hours is considered normal. A blood glucose level of greater than 200 mg/dl at 2 hours is indicative of diabetes. A blood glucose level of 140-200 mg/dl at 2 hours indicates impairment in glucose tolerance.

Three ways to diagnose diabetes are available and each must be confirmed on a subsequent day. Fasting plasma glucose (FPG) is the preferred test because of its lower cost and ease of use. Hyperglycaemia not sufficient to meet the diagnostic criteria for diabetes is categorised as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Impaired fasting glucose is diagnosed in the presence of fasting plasma glucose  $\geq 6.1$  but  $< 7.0$  mmol/l, whereas impaired glucose tolerance implies a plasma glucose value 2 hours after a glucose load (during an OGTT) of  $\geq 7.8$  but  $< 11.1$  mmol/l. Both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease (CVD).

### **2.1.2 Symptoms and complications**

The main symptoms of diabetes are:

- Unexplained weight loss (although appetite often increases)
- Polyphagia (frequently hungry)
- Polyuria (frequently urinating)
- Polydipsia (frequently thirsty)
- Blurred vision
- Severe fatigue
- Poor wound healing (cuts, scrapes etc)

- Dry or itchy skin
- Recurrent infections such as vaginal yeast infections, groin rash, or external ear infections (swimmers ear)

The main complications of diabetes are:

- Atherosclerosis (pathological process leading to cardiovascular disease)

Atherosclerosis can lead to widespread cardiovascular disease including coronary artery disease, cerebrovascular disease and peripheral vascular disease. Diabetes is associated with a two- to three-fold increase in the risk of coronary heart disease and stroke. Cardiovascular disease is also frequently related to hypertension. In type 2 diabetes up to 30% of patients in the UKPDS had hypertension at diagnosis. Nearly all patients will be hypertensive after 5 to 10 years duration, increasing the risk of cardiovascular disease.

- Diabetic kidney disease

Diabetic kidney disease is caused mainly by high blood glucose levels. Due to damage in the small blood vessels in the kidneys, protein is released into the urine. Diabetic kidney disease is often associated with high blood pressure, which may not develop until after the kidneys have been affected. Renal failure is a common effect of diabetes. In the UK 20% of patients entering renal replacement therapy programmes have diabetes as a cause of their renal failure.

- Diabetic retinopathy

Diabetic retinopathy is an eye disease generally associated with long-standing diabetes. It is a major cause of poor vision in the UK and, if left untreated, diabetic retinopathy can lead to blindness. Prolonged periods of high blood sugar levels cause damage to the small blood vessels in the retina at the back of the eye. These blood vessels initially become leaky and may become blocked off. The leakiness causes haemorrhages and exudates (leakage of fats) from the vessels onto the retina. Leakage may also cause swelling (oedema of the retina). Blocked vessels can starve the retina of oxygen, leading to the growth of new abnormal vessels from the retina. Diabetic retinopathy is the most common cause of blindness in people of working age.

- Diabetic neuropathy, leading to foot ulceration and infection

This condition can be either acute or chronic. Neuropathy can affect the nervous system, either as a painful or reduced muscle function (motor control), sense of touch, or function of the inner organs and blood vessels (the autonomic system). There is also a risk of foot ulceration and amputation. Diabetic neuropathy is caused by a prolonged high blood glucose level. Once the blood glucose level rises above a certain point, nerves throughout the body gradually begin to be damaged. About 15% of people with diabetes develop foot ulcers, and 5-15% of people with diabetic foot ulcers require amputations.

- Peripheral vascular disease

Peripheral vascular disease may lead to ischaemia and ultimately gangrene and amputation distally, for example amputation of the feet or legs.

- Susceptibility to infections, for example urinary tract infections
- Hypoglycaemia

Hypoglycaemia occurs when there is a fall in blood glucose levels, and may lead to loss of consciousness. Although it is potentially serious, it is easily treated by oral or intravenous glucose. Patients undergoing therapies that increase the levels of insulin in the blood have increased susceptibility to hypoglycaemia. Each individual's therapy must balance the goal of normoglycaemia against the risk of hypoglycaemia.

- Ketoacidosis (DKA)

Diabetic ketoacidosis develops when there is absolute or relative insulin deficiency, secondary either to omitting insulin or under treatment during an infection or other major stress. Because of the insulin deficiency hyperglycaemia and ketoacidosis develop. Severe high blood glucose and ketoacidosis are serious and potentially life-threatening medical problems which can occur in diabetes. Ketoacidosis is rare in people with type 2 diabetes.

- Hypersmolar non-ketotic coma

This form of acute metabolic disturbance is more common than ketoacidosis in people with type 2 diabetes. A hypersmolar non-ketotic coma occurs when there seems to be sufficient insulin to prevent the breakdown of fat and thus prevent ketoacidosis but where blood glucose levels rise extremely high. The person becomes very dehydrated and hypersmolar.

The risk of chronic complications can be reduced by good blood glucose and blood pressure control, and also aggressive management of cardiovascular risk factors. In addition there is a need for regular screening for early complication of diabetes as early identification may prevent and can certainly slow the progression of complications. Thus early identification of retinopathy can lead to laser treatment and prevention of loss of sight etc.

Diabetic complications are a major cause of morbidity.<sup>3</sup> Estimates of diabetes-related mortality based on death certificate data are seriously misleading, because diabetes will have been a contributory factor in many deaths attributed to other underlying cause. Age and sex specific mortality rates are higher for people with diabetes than for non-diabetic individuals.<sup>4</sup>

## **2.2 EPIDEMIOLOGY**

Diabetes mellitus affects 2.4% of adult population,<sup>3</sup> of whom 200,000 have type 1 diabetes, and more than a million have type 2 diabetes.<sup>5</sup> Without taking into account improved detection, the prevalence of both type 1 and type 2 diabetes will increase over the next two decades. Type 2

diabetes is more common in the elderly population, more prevalent in men than women and varies depending on ethnicity. It has been estimated that the prevalence of type 2 diabetes in the UK will more than double between 1997 and 2010.<sup>6</sup> Diabetes is much more common in people of Asian Indian and Afro-Caribbean origin than people of Caucasian origin. In a Newcastle study,<sup>7</sup> 17.9% of South Asians aged 25-74 years were found to have the disorder, with a further 18.7% having impaired glucose tolerance, which implies a 30-50% higher risk of the development of diabetes in 5-10 years. Weight is another important risk factor for type 2 diabetes. It is estimated that 75% of people who develop type 2 diabetes are, or have been, obese.

### **2.3 CURRENT TREATMENT OPTIONS AND SERVICE PROVISION**

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycaemic control, be addressed.

The goal of insulin treatment is to control the amount of insulin in the bloodstream so that glucose levels are normal or near normal (normoglycaemia). The treatment of diabetes is based on individual needs.

The treatment protocol may include:

- appropriate diet to manage blood glucose level
- exercise to lower and help the body use blood glucose
- regular blood testing for blood glucose levels

The goal of nutrition intervention is to assist and facilitate individual lifestyle and behaviour changes that will lead to improved metabolic control. This addresses not only glycaemic control but also other aspects like dyslipidaemia and hypertension.

Specific treatment is determined based on:

- The patient's age, overall health, and medical history
- Extent of the disease
- The patient's tolerance for specific medications, procedures, or therapies
- Expectations for the course of the disease
- The patient's opinion or preference

The objective of any insulin delivery regimen is to simulate the body's normal secretion of insulin in response to dietary intake, exercise levels and the underlying metabolic state, keeping blood glucose levels as close to normal as possible.

With the help of the healthcare team, people with diabetes will maintain control of their blood glucose, blood pressure and other risk factors that may help to prevent the development of complications. This will maximise their quality of life and reduce the risk of developing long-term complications.

### 2.3.1 Medication

There are a variety of medications, along with insulin formulations, that help people with diabetes achieve adequate blood glucose control. These drugs are described below, including their actions and the role they play in helping people with diabetes attain a healthy blood glucose range.

### 2.3.2 Type 2 therapies

Type 2 diabetes can be managed by diet and exercise alone, at least in its early stages. The purpose of a diet is to reduce energy input in order to promote weight loss, and hence insulin sensitivity. However, type 2 diabetes is a progressive disease. Nearly all patients require oral glucose lowering drugs after some time and most patients eventually need insulin in order to maintain satisfactory blood glucose levels.

Insulin cannot be taken orally, and must therefore be given by injection, usually through the subcutaneous route. The aim of insulin treatment is to achieve the best possible control of blood glucose levels while avoiding hypoglycaemia. There are various types of insulin and possible schedules. The three main types of insulin are classified by the speed of action. Short acting insulin has a relatively rapid onset of action, for example for use immediately following a meal, and includes soluble insulin, insulin lispro and insulin aspart. Intermediate acting insulin is used when longer periods of action are required and includes isophane insulin and insulin zinc suspension. The action of the third type of insulin is slow in onset and lasts for long periods, for example crystalline insulin zinc suspension.

There are four main groups of oral glucose-lowering drugs currently listed in the British National Formulary.<sup>8</sup>

- Sulphonylurea stimulates insulin production in the pancreas and increases insulin sensitivity at the cellular level. Weight gain is the most common side effect; other side effects include skin rash, jaundice, sensitivity to sunlight and hypoglycaemia.
- Metformin increases insulin sensitivity at the cellular level with no effect on the pancreas, eliminating the danger of hypoglycaemia. Side effects include gastrointestinal disorders, usually nausea, vomiting and diarrhoea in up to 30% of patients.
- Alpha-Glucosidase Inhibitors work in the small intestine to slow carbohydrate and glucose absorption. Side effects include nausea, diarrhoea and flatulence.
- Thiazolidinediones are oral glucose-lowering drugs specifically designed for type 2 diabetes. They reduce insulin resistance through the activation of peroxisome proliferator-activated receptor-gamma.

### 2.3.3 Management guidelines

Several clinical practice guidelines for the treatment of type 2 diabetes have been developed recently.<sup>9,10,11,12,13,14,15</sup> These all recommend a 'step-up' policy of treatment, starting with diet and lifestyle advice alone, and adding various oral glucose-lowering agents and eventually

insulin if targets are not achieved. Type 2 diabetes is progressive. Hence, although patients may be adequately managed initially on diet alone, within three years of onset 50% of patients require multiple therapy, and after nine years this figure has increased to 75%.<sup>16</sup>

The guidelines recommend that individual treatment targets should be set, based on the need to achieve good control of blood glucose and cardiovascular risk factors, whilst avoiding the risk of hypoglycaemia and maintaining an acceptable quality of life. The WHO blood glucose cut-offs are designed for diagnosis, and should not be used as therapeutic targets. Commonly used figures for high risk values are shown in Table 1.

**Table 1: Vascular risk assessment guidelines**

	<b>Low risk</b>	<b>At risk</b>	<b>High risk</b>
<b>Blood glucose</b>			
HbA1c (%)	≤6.5	6.5-7.0	>7.0
Venous fasting plasma glucose (mmol/l)	≤6.0	6.0-7.0	>7.0
Self-monitored fasting blood glucose (mmol/l)	≤5.5	5.5-6.0	>6.0
<b>Blood lipids</b>			
Total serum cholesterol (mmol/l)	<4.8	4.8-5.0	>5.0
Serum LDL cholesterol (mmol/l)	<3.0	3.0	>3.0
Serum HDL cholesterol (mmol/l)	>1.2	1.2-1.0	<1.0
Serum triglycerides (mmol/l)	<1.7	1.7-2.2	>2.2
<b>Blood pressure</b>			
Blood pressure (mmHg)	<140/85		>140/80

The commencement of an oral glucose-lowering drug is advocated if blood glucose levels remain high after an adequate trial of life-style education. Initiation of an oral agent is suggested (by the now-outdated European guidelines) when HbA1c >6.5% (FPG>6.0mmol/l), or occasionally (if other risk factors are low) when HbA1c >7.5% (FPG>7.0mmol/l).<sup>15</sup> Attempts to modify lifestyle factors should continue alongside medical treatment.

The choice of initial oral glucose-lowering drug depends upon the patient's weight (metformin is advocated for obese patients) and upon their expected susceptibility to the various side effects. Dose titration is recommended, starting with a low dose and gradually increasing towards the ceiling dose if targets are not met. Dosages should be reviewed and reduced if adverse effects are observed or if blood glucose is well within the target range.

The guidelines differ with respect to the recommended sequence and timing of the next step, after failure with a single oral glucose-lowering agent. Some recommend a trial of another single oral agent, before moving to combination therapy.<sup>9</sup> Other guidelines recommend adding another oral agent to current medication.<sup>12,15</sup> The European guidelines<sup>15</sup> suggest that triple therapy with three differently acting agents may be tried if targets cannot be achieved on the maximum tolerated doses of two drugs.

If blood glucose levels remain high after an adequate trial of oral glucose-lowering drugs then insulin therapy is recommended (unless the patient has a poor life expectancy and is asymptomatic). The European guidelines suggest that, for most patients, insulin should be added to oral medication if HbA1c >7.5% after "maximum attention" to diet and oral medication.<sup>15</sup>

The guidelines also make a range of other recommendations relating to:

- antihypertensive therapy;
- the location and organisation of services (primary/secondary/shared care);
- the professional skills that should be included in diabetes team (general practitioner and practice nurse, consultant physician, diabetes specialist nurse, dietician, chiropodist and other specialists as necessary);
- the need for structured patient education and self-care programmes;
- the need for self-monitoring and regular professional checks to ensure that blood glucose levels are maintained as close to optimal levels as is possible;
- and the need for a range of screening tests to monitor other risk factors, side effects and complications (e.g. blood pressure monitoring, an annual test for urinary protein and microalbuminuria (MA), regular eye and foot checks).

#### **2.3.4 The burden of disease**

Estimates of the financial cost of diabetes vary enormously, depending on whether they include all costs or only health care costs and on whether they include costs of disease associated with or caused by diabetes.<sup>17,18,19,20,21</sup>

The estimated total cost to the NHS, including inpatient, prescription and GP consultation costs, of treating diabetes mellitus (all types) has been estimated at £243m for the UK in 1995/96.<sup>22</sup> This represents in real terms (i.e. inflation adjusted) an increase of around 25% since 1989. Prescriptions make up the largest component of this cost estimate, closely followed by inpatient care (Figure 2). However, this figure only includes the direct cost of treating disease specifically attributed to diabetes. It does not include the cost of treatments where diabetes was a contributory factor.

Another estimate, based on a survey of a district in South Wales,<sup>23</sup> found that the additional hospital costs for people with diabetes was £1,800 per person. This represents 9% of UK hospital costs, around £1.9 billion each year.<sup>24</sup>

## **2.4 DESCRIPTION OF INTERVENTION**

The thiazolidinediones (glitazones) are a recently developed class of oral glucose-lowering drugs.<sup>25,26</sup> They work through the activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) receptors, so reducing insulin resistance.<sup>27</sup> Glitazones are not intended for type 1 diabetes.

There are currently two thiazolidinedione drugs licensed in the UK:

- Rosiglitazone: Avandia (SmithKline Beecham)
- Pioglitazone: Actos (Takeda & Eli Lilly).

The main adverse effect of these drugs is weight gain. There have been some instances of hepatocellular dysfunction, and therefore it is recommended in the Summaries of Product Characteristics<sup>28,29</sup> that patients being treated with these drugs undergo liver function tests every two months during the first year of treatment, and at regular intervals thereafter.

## **2.5 OUTCOME MEASURES**

### **2.5.1 Principal goals of treatment**

The principal aim of treatment in diabetes is the reduction of mortality and morbidity resulting from increased blood glucose levels, while maintaining a good quality of life. HbA<sub>1c</sub> should ideally be  $\leq 7\%$ , but adjusted to accommodate rates of hypoglycaemia acceptable to people living with diabetes. Insulin secretion in non-diabetics is characterised by continuous basal secretion with peaks immediately after meals and steady release throughout the night. Insulin requirements are at a low during early mornings.

### **2.5.2 Glycaemic control**

The Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) demonstrated that HbA<sub>1c</sub> must be reduced to  $< 7\%$  to minimise the development of microvascular complications.

### **2.5.3 Cardiovascular risk factors**

Cardiovascular disease is a major complication and the leading cause of premature death among people with diabetes. Adults with diabetes are two to four times more likely to have heart disease or suffer a stroke than people without diabetes. Blood glucose and blood pressure control are associated with reduced risk of complications. Each 1% reduction in HbA<sub>1c</sub> is associated with reductions of risk of 21% for any endpoint related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction and 37% for microvascular complications.<sup>30</sup> Each 10 mm Hg decrease in systolic blood pressure is associated with reductions of risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction and 13% for microvascular complications.<sup>31</sup>

### **3. CLINICAL EFFECTIVENESS**

#### **3.1 SEARCH STRATEGY**

##### **3.1.1 Sources searched**

12 electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. A list of databases is provided in **Appendix 1**.

In addition, the reference lists of relevant articles were checked and 14 health services research related resources were consulted via the Internet. These included HTA organisations, guideline producing bodies, generic research and trials registers and specialist diabetes sites. A list of these additional sources is given in **Appendix 2**. Finally, citation searches of key papers were undertaken using the Science Citation Index (SCI) citation facility and the reference lists of included studies were checked for additional studies.

##### **3.1.2 Search terms**

A combination of free-text and thesaurus terms were used. 'Intervention' terms included: glitazone(s), thiazole(s), thiazolidinedione, PPAR gamma agonist(s), pioglitazone, actos, 111025-46-8 (CAS registry number), ad 4833 and u 72107 (product codes), rosiglitazone, avandia, 122320-73-4 (CAS registry number), BRL 49653 (product code). Copies of the search strategies used in the major databases are included in **Appendix 3**. Search strategies in electronic format are available on the attached disk.

##### **3.1.3 Search restrictions**

No date, language, study or publication type restrictions were applied.

#### **3.2 CLINICAL EFFECTIVENESS OF ROSIGLITAZONE IN THE TREATMENT OF TYPE 2 DIABETES**

##### **3.2.1 Background**

This report is an update of the review undertaken by Lord and colleagues.<sup>32</sup> Tables 1 and 2 summarise the results of the meta-analyses undertaken for the original review, examining the effectiveness of the two licensed doses of rosiglitazone (4mg and 8mg) as a combination therapy (with metformin or sulphonylurea). In addition, the evidence provided by the additional trials is appended to the appropriate table.

Overall, a meta-analysis of trials showed that the addition of rosiglitazone to metformin and sulphonylurea led to significantly greater reductions blood glucose over six months, with a higher response rate than placebo therapy. Rosiglitazone combination therapy was found to increase beta-cell function and, at high doses, to decrease significantly insulin resistance compared to placebo combinations.

The addition of rosiglitazone led to significantly higher increases in HDL and LDL cholesterol over six months compared to metformin alone. This was also true when compared to sulphonylurea therapy in most cases, however changes in HDL levels were not significantly

different for the 4mg group. At six months, there was no significant difference in HDL cholesterol levels. The 4mg dose had an insignificant effect on LDL cholesterol levels, but the 8mg dose produced significantly higher levels of LDL cholesterol at six months. Some data suggest that the initial increase in LDL cholesterol seen with rosiglitazone stabilises, whereas HDL cholesterol continues to increase over 18 months. This reduction appears to be statistically significant for the rosiglitazone/metformin group but not for the rosiglitazone/sulphonylurea group.

There were no significant differences between treatment and control groups of either drug in blood pressure at six months. Although increases in body weight were significantly greater for the rosiglitazone/metformin combination therapy groups compared to the metformin control groups, there were no significant absolute differences between the groups in body weight at six months. The rosiglitazone/sulphonylurea combination groups showed significantly greater weight increases over six months than the sulphonylurea control groups.

There was no significant difference between the rosiglitazone/metformin combination groups compared to the metformin group in terms of the proportion of patients who experienced at least one adverse event, withdrew from the studies because of an adverse event, or withdrew for any reason. There was also no significant difference in the incidence of adverse events for the sulphonylurea combination arms compared to the control arms, however significantly lower proportions of patients withdrew in the 8mg rosiglitazone/sulphonylurea combination groups compared to the controls.

The addition of rosiglitazone to therapy was associated with a significant reduction in the risk of hyperglycaemia in the case of metformin, however there was no significant effect in the case of sulphonylurea. Significant increases in the incidence of hypercholesterolaemia and hyperlipaemia were observed with rosiglitazone/sulphonylurea therapy compared to sulphonylurea alone. For rosiglitazone/metformin combination therapy, a significant increase in hyperlipaemia (but not hypercholesterolaemia) was observed. Rosiglitazone/metformin therapy compared to metformin alone was associated with a reduction in the incidence of hypertension and diarrhoea. The incidence of anaemia and oedema was higher for the rosiglitazone combination therapies than for the controls. No other significant differences were noted between rosiglitazone and placebo arms in the area of adverse events.

### **3.2.2 New Studies**

In this section we critically review the new evidence on the effectiveness of rosiglitazone identified through the search strategy described above or submitted by the sponsor (GSK), and compare them to the estimates in the previous report.<sup>32</sup>

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

Three additional study reports were identified in the searches of the published literature. One of these reported the results of the Mexican arm of study 044 (which was submitted to the Institute by the sponsor in confidence),<sup>33</sup> which is reviewed below. Therefore we do not consider this

paper separately. A second report<sup>34</sup> had a JADAD score of 0 and therefore is not considered further. The third study, by Raskin and colleagues<sup>35</sup> examines the use of rosiglitazone in subjects treated with insulin. This paper does not appear to be based on any of the previously reported studies and is therefore reviewed below.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

### **Raskin et al: A randomised trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated Type 2 Diabetes<sup>35</sup>**

This three armed study randomised 319 patients between insulin plus placebo, insulin plus rosiglitazone 4mg and insulin plus rosiglitazone 8mg. The primary outcome measure was the change in HbA1c at 26 weeks compared to baseline. (The mean baseline measurement was  $8.9 \pm 1.1$  to  $9.1 \pm 1.3$ .) The mean difference in the HbA1c change from baseline was  $-0.7\%$  for the low dose rosiglitazone group and  $-1.2\%$  for the high dose rosiglitazone group. Compared to baseline, the mean insulin dose for the low dose rosiglitazone reduced by 5.6 units, compared to 0.6 units for the placebo group. The mean insulin dose in the high dose rosiglitazone group reduced by 12 units.

#### **3.2.3 Summary of new evidence on rosiglitazone**

The additional studies confirm the efficacy of rosiglitazone as described in the original review by Lord et al.<sup>32</sup>

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### **3.2.4 Legend:**

WMD (95% CI fixed): weighted mean difference (95% confidence interval fixed)

HbA1c: values given as percentage differences in HbA1c change between trial and placebo arms

FPG: fasting plasma glucose; values given as mmol/l difference in FPG change between arms

Cholesterol: values given as mmol/l difference in cholesterol change between arms

BP: blood pressure; values given as mmHg difference in BP change between arms

Weight: values given in kg as difference in weight gain between arms

N: number of patients in study

N/A: not applicable; information not given in study reviewed

To convert from mg/dl to mmol/l reported figures were multiplied by 0.0555.

“Original Report” refers to a meta-analysis of studies reviewed in the original review by Lord et al.<sup>32</sup>

**Table 2a: Effectiveness of Rosiglitazone 4mg with Metformin**

	Original Report	Study 044
	WMD (95% CI Fixed)	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>
HbA1c	-0.75 (-1.17, -0.33)	
FPG	-2.13 (-2.95, -1.31)	
HDL Cholesterol	0.12 (0.04, 0.20)	
LDL Cholesterol	0.33 (0.08, 0.58)	
BP Systolic	-2.10 (-5.96, 1.76)	
BP Diastolic	-0.90 (-3.40, 1.60)	
Weight	1.90 (1.17, 2.63)	

Note: confidence intervals were not available for some results. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

**Table 2b: Effectiveness of Rosiglitazone 4mg with Sulphonylurea**

	Original Report	Study 128 (N=53)	Study 132
	WMD (95% CI Fixed)	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>
HbA1c	-1.08 (-1.30, -0.86)		
FPG	-2.58 (-3.03, -2.14)		
HDL Cholesterol	0.05 (0.01, 0.08)		
LDL Cholesterol	0.27 (0.17, 0.36)		
BP Systolic	N/A		
BP Diastolic	N/A		
Weight	2.35 (1.86, 2.83)		

Note: confidence intervals were not available for some results.

**Table 3a: Effectiveness of Rosiglitazone 8mg with Metformin**

	Original report	Study 044
	WMD (95%CI Fixed)	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>
HbA1c	-0.88 (-1.18, 0.57)	
FPG	-2.75 (-3.38, -2.13)	
HDL Cholesterol	0.13 (0.07, 0.20)	
LDL Cholesterol	0.29 (0.11, 0.47)	
BP Systolic	-0.07 (-2.89, 2.75)	
BP Diastolic	-1.59 (-3.32, 0.13)	
Weight	3.33 (2.68, 3.98)	

Note: confidence intervals were not available for some results.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

**Table 3b: Effectiveness of Rosiglitazone 8mg with Sulphonylurea**

	Study 132
	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>
HbA1c	
FPG	
HDL Cholesterol	
LDL Cholesterol	
BP Systolic	
BP Diastolic	
Weight	

Note: no results available from previous meta-analysis for this combination

**Table 4: Methodological Quality of new trials submitted by Sponsor**

JADAD CRITERIA	STUDY 044	STUDY 085	STUDY 108	STUDY 128	STUDY 132	STUDY 134	STUDY 136	Raskin et al Diabetes Care July 2001
A1	<i>Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.</i>							Y
A2								A
B1								A
C1								Y
C2								Y
C3								Y
C4								Y
D1								N
D2								Y
D3 dropouts								
JADAD								4
Sample size achieved?								

**Legend :**

A1 : Was the trial described as “randomised” ?

A2 : Was allocation random (A), quasi-random (B), systematic (C), or not stated or unclear (D)?

B1 : Was concealment adequate (A), inadequate (B), or unclear (C)?

C1 : Was the trial described as “double-blind”?

C2 : Was the treatment allocation masked from the participants?

C3 : Was the treatment allocation masked from the investigators?

C4 : Was the treatment allocation masked from the outcome assessments?

D1 : Were the number of withdrawals in each group stated?

D2 : Was an intention-to-treat analysis performed?

D3 : What were the drop-out rates in each group of the trial for each of the main outcomes? (Drop-out rates are given for each trial in the three rows below D3.)

Y: yes

N: no  
U: unclear  
INS : insulin  
P : placebo  
RSG : rosiglitazone  
ATV : atorvastatin  
SU : sulphonylurea

### **3.3 CLINICAL EFFECTIVENESS OF PIOGLITAZONE IN THE TREATMENT OF TYPE 2 DIABETES**

#### **3.3.1 Background**

The clinical effectiveness of pioglitazone was reviewed by Chilcott et al. for National Institute of Clinical Excellence in March 2001.<sup>4</sup>

#### **3.3.2 Summary of evidence reviewed by Chilcott et al.**

Eleven studies were included in the previous review. Of these, seven referred to pioglitazone as a monotherapy in trials of placebo versus various doses of pioglitazone, and hence are not relevant to this analysis. One study was kept in confidence and is therefore not reviewed here. The remaining studies included study PNFP-010 comparing sulphonylurea with placebo to sulphonylurea with 15mg or 30mg pioglitazone daily, study PNFP-014 comparing insulin with placebo to insulin with pioglitazone 15mg and 30mg (contrary to indication in the SmPC, which contra-indicates combination therapy with insulin) and study PNFP-027 comparing metformin with placebo to metformin with pioglitazone 30mg.

**Table 5: Studies identified in the previous review**

Study	Subjects	Treatment groups (no. randomised)	Study procedure	Outcomes reported
PNFP-010	Type 2 diabetics, aged 30-75 years, treated with sulphonylureas alone or with acarbose or metformin. HbA1c >8% at screening and randomisation, fasting C peptide >1 ng/ml	S + placebo (187) S + P 15mg/day (184) S + P 30mg/day (189)	2 week screening period, then 4 weeks on S + placebo, then 16 weeks on allocated treatment. Patients were maintained on previous dose of sulphonylurea.	HbA1c, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight
PNFP-014	Type 2 diabetics, treated with insulin >30 units/day for at least 30 days. HbA1c >8% at screening and randomisation, fasting C peptide >0.7 ng/ml.	Insulin + placebo (187) I + P 15 mg/day (191) I + P 30 mg/day (161)	2 week screening period, then 4 weeks on I + placebo, then 16 weeks on allocated treatment. 'No attempt made to change insulin regimen.'	HbA1c, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight
PNFP-027	Type 2 diabetics, treated with metformin for >30 days. HbA1c >8% at screening and randomisation, fasting C peptide >1 ng/ml	Metformin + placebo (153) M + P 30 mg/day (161)	2 week screening period, then four weeks on M + placebo, then 16 weeks on allocated treatment	HbA1c, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight

Information was available on the characteristics of the study populations in studies PNFP-010, PNFP-014 and PNFP-027. No information was available on comorbidities of patients recruited to PNFP-010 or PNFP-027. There were no statistically significant differences in baseline characteristics between the study groups in either study. In the former study, 30/187, 29/184 and 23/189 patients were withdrawn from the placebo, 15 mg and 30 mg arms respectively. Of these, lack of efficacy was the reason in 13, 12 and 4 patients respectively (FDA website).

A meta-analysis of results was not appropriate for the pioglitazone studies because each trial evaluated pioglitazone in combination with a different drug. All studies took place over a period of 16 weeks.

When used in combination with metformin, sulphonylurea or insulin, pioglitazone, at doses of 15 mg or 30 mg daily led to a significant fall in blood glucose and HbA1c. The effect was greater at the higher than the lower dose. The extent of the fall in HbA1c was between 0.64 and 1.26 percentage points. Because the full fall in blood sugar took 8 (studies PNFP-010, PNFP-014) to 12 (study PNFP-027) weeks, the HbA1c changes at 16 weeks may not fully reflect the fall in blood glucose and so underestimate the overall effect. This effect is maintained for at least 40 weeks. Secondary analysis suggests that the effect was greater in women than in men, and was also greater in those with a higher than those in a lower initial HbA1c level.

**Table 6: Effect of pioglitazone (P) on HbA1c (%) in combination therapy**

<b>PNFP-010</b>	<b>Sulphonylurea + placebo</b>	<b>Sulphonylurea + P 15mg/day</b>	<b>Sulphonylurea + P 30mg/day</b>
<b>Baseline</b>	9.86	10.01	9.93
<b>Mean change</b>	0.06	-0.82	-1.22
<b>Least squares (LS) mean difference between placebo and P arms</b>		-0.88 (Confidence Interval (CI) -1.17 to -0.58)	-1.28 (CI -1.57 to -0.99)
<b>PNFP-014</b>	<b>Insulin + placebo</b>	<b>Insulin + P 15mg/day</b>	<b>Insulin + P 30mg/day</b>
<b>Baseline</b>	9.75	9.75	9.84
<b>Mean change</b>	-0.26	-0.99	-1.26
<b>LS mean difference between placebo and P arms</b>		-0.73 (CI -1.00 to -0.47)	-1.00 (CI -1.27 to -0.74)
<b>PNFP-027</b>	<b>Metformin + placebo</b>		<b>Metformin + P 30mg/day</b>
<b>Baseline</b>	9.77		9.92
<b>Mean change</b>	0.19		-0.64
<b>LS mean difference between placebo and P arms</b>			-0.83 (CI -1.15 to -0.51)

There was a significant fall in both fasting C peptide and insulin levels on pioglitazone combination treatment in studies PNFP-010 and PNFP-027. In study PNFP-014 (pioglitazone combined with insulin treatment), the fall in fasting C peptide levels was significant for the 15mg pioglitazone group, but not the 30mg group.

The level of triglyceride in the 30mg pioglitazone combination group was significantly reduced compared to the placebo combination group in each of the three trials, with a fall of the order of 0.3 mmol/l. High density lipoprotein levels increased in pioglitazone combination treatment

groups as compared to placebo combination groups. There was no change in total cholesterol or LDL cholesterol levels.

**Table 7: Effect of pioglitazone (P) on HDL cholesterol (mmol/l) in combination therapy<sup>36</sup>**

<b>PNFP-010</b>	<b>Sulphonylurea + placebo</b>	<b>Sulphonylurea + P 15mg/day</b>	<b>Sulphonylurea + P 30mg/day</b>
<b>Baseline</b>	1.11	1.07	1.08
<b>Mean change</b>	-0.03	0.04	0.10
<b>LS mean difference between placebo and P arms</b>		0.06 (CI 0.02 to 0.11)	0.13 (CI 0.08 to 0.17)
<b>PNFP-014</b>	<b>Insulin + placebo</b>	<b>Insulin + P 15mg/day</b>	<b>Insulin + P 30mg/day</b>
<b>Baseline</b>	1.10	1.12	1.11
<b>Mean change</b>	-0.02	0.06	0.07
<b>LS mean difference between placebo and P arms</b>		0.07 (CI 0.02 to 0.13)	0.09 (CI 0.03 to 0.14)
<b>PNFP-027</b>	<b>Metformin + placebo</b>		<b>Metformin + P 30mg/day</b>
<b>Baseline</b>	1.09		1.11
<b>Mean change</b>	0.00		0.08
<b>LS mean difference between placebo and P arms</b>			0.08 (CI 0.03 to 0.13)

**Table 8: Effect of pioglitazone (P) on LDL cholesterol (mmol/l) in combination therapy<sup>36</sup>**

<b>PNFP-010</b>	<b>Sulphonylurea + placebo</b>	<b>Sulphonylurea + P 15mg/day</b>	<b>Sulphonylurea + P 30mg/day</b>
<b>Baseline</b>	3.22	3.22	3.28
<b>Mean change</b>	0.15	0.08	0.13
<b>Least squares mean difference</b>		-0.08 (CI -0.23 to 0.08)	-0.02 (CI -0.18 to 0.14)
<b>PNFP-027</b>	<b>Metformin + placebo</b>		<b>Metformin + P 30mg/day</b>
<b>Baseline</b>	3.06		3.09
<b>Mean change</b>	0.07		0.18
<b>LS mean difference between placebo and P arms</b>			0.11 (CI -0.03 to 0.24)

Unfortunately, the table with details of the LDL levels in study PNFP-014 appears to have been misprinted in the statistical review on the FDA website. The results are therefore not reproduced here.

The changes seen at 16 weeks – a fall in triglycerides and an increase in HDL – are maintained at 40 weeks in both the metformin and sulphonylurea combination studies.<sup>37</sup> There is no further change in lipid levels at 40 weeks over that reported at 16 weeks. The changes seen at 16 weeks – a fall in triglycerides and an increase in HDL – are maintained at 40 weeks in both the metformin and sulphonylurea combination studies.<sup>37</sup> There is no further change in lipid levels at 40 weeks over that reported at 16 weeks.

While there is no direct evidence available on the effect of pioglitazone on diabetic complications, including cardiovascular mortality, there is evidence from the UKPDS study<sup>38,39,31</sup> that improved glycaemic control reduces the incidence of microvascular complications, so it would not be unreasonable to expect that this would hold true if the improved glycaemic control is achieved through using pioglitazone.

There is evidence from the clinical trials that pioglitazone does have an impact on recognised cardiovascular risk factors. When pioglitazone is used in combination therapy there is a consistent fall in triglycerides when doses of 30mg or more are used, and also a statistically significant increase in HDL levels. These changes are achieved within 8 weeks of treatment, and could be expected to lead to a reduction in cardiovascular risk, other things being equal.

Any consequent reduction in cardiovascular risk will, however, be countered by the increased risk associated with the significant and progressive weight gain observed on treatment. In the combination studies, body weight increased significantly in the pioglitazone groups compared to the placebo groups. The treatment differences from placebo were related to the dose of

pioglitazone administered and were greater when pioglitazone was combined with insulin or sulphonylurea than when it was combined with metformin.

**Table 9: Effect of pioglitazone (P) on bodyweight (kg) in combination therapy**

<b>PNFP-010</b>	<b>Sulphonylurea + placebo</b>	<b>Sulphonylurea + P 15mg/day</b>	<b>Sulphonylurea + P 30mg/day</b>
<b>Mean change</b>	-0.83	+2.18	+3.06
<b>PNFP-014</b>	<b>Insulin + placebo</b>	<b>Insulin + P 15mg/day</b>	<b>Insulin + P 30mg/day</b>
<b>Mean change</b>	-0.11	+2.53	+3.92
<b>PNFP-027</b>	<b>Metformin + placebo</b>		<b>Metformin + P 30mg/day</b>
<b>Baseline</b>	93.96		93.24
<b>Mean change</b>	-1.06		+1.41
<b>LS mean difference between placebo and P arms</b>			2.48 (CI 1.72 to 3.23)

A significant safety concern associated with pioglitazone was the possibility that it might be associated with hepatitis in the same way that troglitazone was. In the studies reviewed by the FDA, the reported incidence of elevation of alanine transaminase greater than three times the upper limit of normal was no different between pioglitazone treated patients and placebo. At 0.26% it was lower than the reported rate in troglitazone-treated patients in controlled trials (1.90%), and therefore is in line with the reported rate in other diabetic agents. However, the relatively small number of patients with long-term exposure to pioglitazone means that a long-term tendency to produce hepatitis cannot be ruled out. Such a tendency would be plausible if the hepatotoxicity of pioglitazone were equivalent to that of troglitazone on a weight-for-weight basis (bearing in mind that the therapeutic dose of troglitazone is much greater than pioglitazone, so that the net exposure was greater for that drug).

Other possible adverse events relate to oedema, haemoglobin, creatinine phosphokinase (CPK) elevation and hypoglycaemia. Oedema is more commonly reported as an adverse event in patients treated with pioglitazone than with placebo in both the monotherapy and combination therapy trials.<sup>4</sup> The overall figures quoted on the FDA website for oedema are 6.6% for pioglitazone treated patients and 2.3% for placebo treated patients. There is a consistent, but not clinically significant, fall in haemoglobin in patients treated with pioglitazone, in the order of 0.38 g/dl. New electrocardiograph (ECG) findings were equally distributed between pioglitazone and placebo treated patients. (One patient, in study PNFP-026, was noted to have developed left ventricular hypertrophy and left bundle branch block on the ECG, which resolved when the drug was withdrawn. Five other patients were noted to have cardiomegaly on x-ray.) Seven male patients in the studies were reported to have CPK values greater than ten times the normal upper limit. Four normalised on the drug, two off the drug, and one had falling, but not yet normal, levels on follow-up. As noted earlier, weight gain is a worrying side effect of pioglitazone treatment. It was reported in many of the studies reviewed in this report.

### 3.3.3 New evidence

For this review Takeda provided a full trial report for one study not included in the original review.<sup>29</sup> This study examined pioglitazone as a monotherapy and is not therefore considered in this review. In addition, Takeda forwarded a list of 50 public domain abstracts and papers related to the efficacy of pioglitazone.

Three clinical effectiveness studies were identified in the information sent by Takeda, or through the search strategies described above.<sup>29,40,41</sup> Comparison of these published papers with the information provided in the previous report established that two of these papers<sup>40,41</sup> were reviewed in the original review, as studies PNFP-010, and PNPF-027. Thus only one additional effectiveness study for pioglitazone has been identified. This study, by Miyazaki and colleagues is reviewed below.

**Miyazaki Y, Mahankali A Matsuda M et al: Improved Glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with Pioglitazone, Diabetes Care 2001;24(4):710-719**

This study is described as a double blind placebo controlled parallel group study. However, insufficient information is given about the randomisation and concealment processes, resulting in a low JADAD score of 2. The study randomised 23 patients already receiving stable doses of a sulphonylurea to receive either pioglitazone 45mg per day, or placebo, for 16 weeks. From the published trial report it is unclear whether this is in combination with the sulphonylurea. However, the abstract supplied by Takeda indicates that this was a combination study. The primary outcome measures were fasting plasma glucose and mean plasma glucose during oral glucose tolerance test. The increases from baseline in body weight, BMI, fat mass and percentage body fat were significantly greater for the pioglitazone group compared to the placebo group. The pioglitazone group also had significantly greater reductions in HbA1c, fasting blood glucose and tryglicerides.

Such a small trial adds little to the evidence base on the efficacy of the pioglitazone. The summary of the evidence on clinical effectiveness described by Chilcott and colleagues still stands; i.e.

“In combination therapy, pioglitazone appeared to be effective in reducing blood glucose in patients with poorly controlled type 2 diabetes. When used in combination with metformin, sulphonylurea or insulin, pioglitazone led to a significant fall in blood glucose and glycalated haemoglobin (HbA1c) at high and low doses, with greater effect at the higher than at the lower dose. Pioglitazone treatment is associated with significant weight gain in the short term, which appears to be greater than that seen with other thiazolidinediones. It also appears to be greater than that seen with sulphonylurea or insulin treatment in the UKPDS, which in turns was greater than that seen on metformin treatment. This weight gain continues, albeit at a lesser rate, for more than a year.”

### **3.3.4 Additional new evidence**

After submission of the assessment report, Takeda provided NICE with the results of four new trials of pioglitazone in type 2 diabetes. Due to the late arrival of these trials, the trial results were not included in this review. However, these trials were provided in time for them to be considered by the NICE Appraisal Committee.

## **3.4 A COMPARISON OF THE CLINICAL EFFECTIVENESS OF ROSIGLITAZONE AND PIOGLITAZONE**

We identified one retrospective medical records study which attempted to compare the clinical effectiveness of the two therapies.<sup>42</sup>

Boyle and colleagues randomly selected 3175 patient records of adults with type 2 diabetes who received either pioglitazone or rosiglitazone between 1<sup>st</sup> August 1999 and 31<sup>st</sup> August 2000. After review with well defined inclusion criteria, 1115 records were included used in an comparison of changes in tryglicerides, total cholesterol, HDL cholesterol, LDL cholesterol and HbA1c between the two treatments. Triglyceride reduction was significantly greater in the pioglitazone group than the rosiglitazone group. Rosiglitazone was associated with an increase in total cholesterol, whilst total cholesterol was significantly reduced in the pioglitazone group. HDL cholesterol was similar between the two groups at follow-up but LDL cholesterol was significantly reduced in the pioglitazone group, whilst it was significantly increased in the rosiglitazone group. The reduction in HbA1c was almost identical between the two groups.

In general, these findings were broadly supported by the results of the studies reviewed here, although no formal analysis was performed.

Whilst these results point to potential advantages in the use of pioglitazone compared to rosiglitazone, it must be remembered that this evidence is taken from a retrospective review of records. Prospective randomised controlled trials would be necessary to establish the relative advantages and disadvantages of the two therapies.

### **Conclusions**

The clinical evidence available showed that glitazones reduce HbA1c by approximately 1%, and are more effective at higher doses than at lower doses. There is significant weight gain associated with glitazone treatment. No data were available on the long-term effects of glitazone use. No prospective randomised controlled trials were found comparing pioglitazone to rosiglitazone, but the available evidence showed that the two treatments had similar effects.

## 4. ECONOMIC ANALYSIS

### 4.1 OVERVIEW OF ECONOMIC ASSESSMENT

The aim of this chapter is to assess the cost-effectiveness of both pioglitazone and rosiglitazone in the treatment of type 2 diabetes. The economic analysis includes a systematic review of the cost-effectiveness literature relating to pioglitazone and rosiglitazone and a review of the economic analyses submitted to the National Institute for Clinical Excellence (NICE) by the sponsoring bodies, Takeda and GlaxoSmithKline.<sup>29,28</sup> In addition modelling literature concerning the treatment of type 2 diabetes mellitus is reviewed in order to determine the appropriateness of the Takeda and GlaxoSmithKline economic models. Finally, the two economic models are compared and the differences between them discussed.

Pioglitazone and rosiglitazone are antihyperglycaemic drugs. They are both indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated.

In the original submission regarding glitazones, NICE recommended to the NHS that patients whose blood glucose levels were not controlled with either metformin or a sulphonylurea alone should be offered metformin and a sulphonylurea in combination, unless there were reasons of contraindications or intolerance. Patients should be offered a glitazone in combination with metformin or sulphonylurea (as an alternative to injected insulin) if they are unable to take metformin and sulphonylurea as a combination therapy, or if their blood glucose level remains high despite adequate trial of this combination treatment. The combination of glitazone and metformin is preferred to the combination of glitazone and sulphonylurea – particularly for obese patients. Glitazone plus sulphonylurea may be offered to patients who are unable to take metformin.

After the original submissions and the NICE guidance for the glitazones, issues have been raised from the drug companies concerning the treatment pathways followed. In particular, it was suggested that adding a glitazone after failure of metformin monotherapy is a better treatment strategy than adding a sulphonylurea. Economic evaluation for this comparison of scenarios has been provided by the drug companies in the current submission. Moreover, it was suggested that the NICE proposal of adding sulphonylurea after metformin monotherapy and then switching to glitazone if the combination therapy fails is not followed in practice by clinicians. The reason is that an immediate substitution of sulphonylurea with glitazone in combination therapy with metformin results in significant loss of glycaemic control. As a result of that, clinicians tend to proceed to triple therapy with metformin, sulphonylurea and glitazone for some time before progressing to combination of metformin with glitazone. Triple therapy is neither licensed nor recommended by NICE. However, it is applied in practice and it is an issue that has been raised since the original submission. Economic evaluation has not been provided by any of the two pharmaceutical companies for this issue.

## 4.2 METHODS

A systematic literature search was undertaken for economic assessments of pioglitazone and rosiglitazone. In addition to the searches conducted for clinical effectiveness, searches were conducted in NHS EED and OHE HEED specifically to identify cost effectiveness literature (**Appendix 3**). This was supplemented by searches in Medline for economic and quality of life literature relating to the costs of insulin therapy (refer to **Appendix 4** for the methodological search filters used).

A broader topic search was undertaken for economic or model-based assessments within diabetes. This search was used to identify assessments that attempt to estimate the long-term impact of glucose-lowering treatments in type 2 diabetes mellitus and that do not limit their scope to individual complications of diabetes. The purpose of this topic review was to generate classification criteria for the evaluation of submitted economic evidence. A generic proforma for the critical appraisal of modelling studies in health economics is used in systematically reviewing studies identified. This is supplemented by a detailed review of the disease-specific factors within all modelling studies identified. Where possible, key outcomes are compared. The key outcomes reported within these studies are:

- Mean lifetime risk of complication;
- Cost per LYG;
- Years free from first significant complication;
- Estimated incidence of complication;
- Total lifetime costs for diabetes;
- Duration of stay in given health state.

## 4.3 RESULTS OF TOPIC REVIEW FOR ISSUES IN HEALTH ECONOMIC MODELLING OF DIABETES

The topic search for economic or model-based studies identified 81 studies relating to the treatment of complications associated with type 2 diabetes. Details of the studies are available from the authors. Five of the studies identified focussed on glucose controlling interventions and addressed multiple complications of diabetes,<sup>43,44,45,46,47</sup> these studies are summarised in Table 10 and in the original appraisal of pioglitazone.<sup>36</sup> Of the five published studies (five publications, four studies), three studies focused on type 2 diabetes mellitus; the remaining two studies focused on type 1 diabetes.

**Table 10: Summary of classification of studies reviewed**

Author	Study Design	Economic Outcomes	Intervention Type	Intervention	Scope
Eastman et al. 43	Modelling	Cost-effectiveness & Cost-utility	Glucose control	Conventional Vs. Intensive Therapy	Type 2
Palmer et al. 44	Modelling	Cost-effectiveness	Glucose control and Screening	ACE Inhibitors, Conventional and Intensive Insulin Therapy	Type 1
Vijan et al. 46	Modelling	None	Glucose control	Hypothetical	Type 2
DCCT 45	Modelling/ cost of illness	Cost-effectiveness & Cost-utility	Glucose control	Conventional Vs. Intensive Therapy	Type 1
Bagust 47	Modelling/ Burden of illness	Cost	Glucose control	Conventional Vs. Intensive Therapy, Diabetics Vs Non-Diabetics	Type 2

The key clinical events within the above models of diabetes are identified below.

- Nephropathy
- Retinopathy
- Acute myocardial infarction (AMI)
- Stroke
- Amputation
- Hypoglycaemia
- Ketoacidosis
- Lactic acidosis

#### **4.3.1 Other important events held within the models**

- Known epidemiology
- Effects of interventions
- Death from non-specific causes

## **4.4 PIOGLITAZONE**

### **4.4.1 Results of Systematic Search for Economic Studies of Pioglitazone**

There are no published studies investigating the health economics of pioglitazone or, indeed, of any other TZD. The only available economic evidence concerning pioglitazone is that obtained

as part of the confidential submission by the sponsoring body, Takeda U.K.<sup>29</sup> *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

It should be noted that the economic model provided in the Takeda update submission is the same as was reviewed in the original appraisal of pioglitazone.<sup>36</sup> Therefore the review that is reported here is taken directly from the original economic review of pioglitazone.<sup>36</sup>

#### **4.4.2 Critical Appraisal of The Economic Submission for Pioglitazone**

A structured proforma was used in the critical appraisal of the economic submission for pioglitazone<sup>48</sup>. To determine how the unpublished submission compares with published models in diabetes the same proforma was used to summarise the five studies identified in table 10.<sup>43,44,45,46,47</sup> A detailed discussion of some of the key factors is given below.

##### **4.4.2.1 Statement of the problem**

The study<sup>29</sup> contains a clear statement of the problem, that is to estimate the impact of 'the effects on HbA1c, total cholesterol and HDL cholesterol in type 2 patients' of treatment with pioglitazone combination therapy (added to either metformin or sulphonylureas) compared with other combination therapies or changing to insulin.

The population of interest is defined as those people with type 2 diabetes whose blood glucose levels are poorly controlled with oral monotherapy with either metformin or sulphonylureas.

The comparator therapies are well defined insofar as intensive glucose control is now accepted as conventional therapy.

The study focuses on the possible lifetime clinical and economic outcomes. The key economic results are reported in terms of the cost per life year gained.

The perspective of the analysis is on direct medical costs with a specific focus on the UK NHS costs.

Clinical benefits are discounted at 1.5%, and costs are discounted at 6%.

##### **4.4.2.2 Cohort information**

One of the key distinctions between the models is the focus on either type 1 or type 2 diabetes mellitus; given the different natural epidemiology of onset the cohort data will vary significantly between models. It is known that type 1 disease has a significantly earlier onset than type 2 disease. As the study by Palmer et al.<sup>44</sup> and the DCCT<sup>45</sup> considered the cost implications of type 1 diabetes, the age range of patients in the cohort is significantly lower than that of patients used in the models proposed by Eastman et al.,<sup>43,49</sup> Vijan et al.<sup>46</sup>. The cohorts used in the models are described in Table 11.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

**Table 11: Cohort information used within the published models**

Author	Disease Type	Cohort Age Range (years)	Source of Cohort Information	No. of Patients in Cohort
Eastman et al. <sup>43</sup>	Type 2	25 – 74	WESDR	10,000
Palmer et al. <sup>44</sup>	Type 1	19 (mean)	Not stated	Not stated
DCCT study <sup>45</sup>	Type 1	13 – 39 (2 cohorts)	WESDR	10,000
Vijan et al. <sup>46</sup>	Type 2	45 – 75 (assumed)	REP, WESDR	Not stated
Bagust <sup>47</sup>	Type 2	Not stated	WESDR, UKPDS	Not stated

*WESDR: Wisconsin Epidemiologic Study of Diabetic Retinopathy*

*REP: Rochester Epidemiology Project, Minnesota*

The patient populations used within the models proposed by Eastman et al.<sup>43</sup> used 10,000 patients as a baseline cohort. From this, 30.5%, 21.7%, 17.7% and 30% were within the age groups 25-44, 45-54, 55-64 and 65-74 respectively. The cohort used in the model by the DCCT<sup>45</sup> also uses 10,000 patients. Equal proportions of males and females were included, and patients were weighted by ethnicity. The mean age of model entry at clinical diagnosis of type 2 diabetes in the US was 51 years. The patient population, included in the two cohorts of patients in the model proposed by the DCCT,<sup>45</sup> consists of a sample of patients with type 1 diabetes in the US who were considered eligible for enrolment in the DCCT (dependent on demographic and clinical characteristics). These two cohorts are classified as follows:

Patients in the conventional treatment arm (primary cohort) had no experience of retinopathy or MA, and a duration of disease of between one and five years.

Patients in the intensive treatment arm had minimal to moderate nonproliferative retinopathy, excreted less than 200mg of albumin in the urine per day and had a duration of diabetes of between one and fifteen years. It was assumed that approximately 17% of the US population would be eligible for enrolment.

It is important to note that the individual characteristics assigned to the patients in the DCCT model will differ significantly from those of the Eastman et al.<sup>43,49</sup> model given the difference in disease type.

The patient population entering the model by Vijan et al.<sup>46</sup> is assumed to have an age range of 45 to 75 years; however this is not explicitly stated within the literature. Patients within the cohort were assumed to have no clinically detectable microvascular complications at the time of diagnosis of diabetes. Patients who present with complications are already declared to be at high risk and, therefore, should be considered for intensive control. The study by Palmer et al.<sup>44</sup> focuses on male type 1 diabetes mellitus patients in Switzerland. The age of this representative cohort was 19 years as this is known to be the median age of onset of type 1 diabetes in Swiss males. This presents a limitation for the Palmer model, as it does not recognise significantly the individual characteristics of the cohort.

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#### 4.4.2.3 Model structure and scope

The models by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> use a Monte Carlo technique. These two models take the form of a micro-simulation Markov model with a one-year cycle, whereby patients enter the simulation as individuals rather than as a cohort. Upon beginning the simulation, patients are assigned individual characteristics, weighted to the incident cases of clinically diagnosed patients with type 2 diabetes in the US population, between the eligible age range criteria (type 1 diabetes in the DCCT study). The eligible age ranges used in these models are shown in cohort information given in Table 12 below.

**Table 12. Types of Modelling used by the Studies**

<b>Author</b>	<b>Type of Simulation</b>	<b>Type of Model</b>	<b>Decision Analysis</b>	<b>Monte-Carlo</b>
Eastman et al. <sup>43,49</sup>	Micro	Markov	Yes	Yes
Palmer et al. <sup>44</sup>	Micro (assumed)	Markov	Yes	Not stated
Vijan et al. <sup>46</sup>	Micro (assumed)	Markov	Yes	Not stated
DCCT <sup>45</sup>	Micro	Markov	Yes	Yes
Bagust <sup>47</sup>	<u>None</u>	<u>Markov</u>	<u>Yes</u>	<u>No</u>

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The models by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> reflect the typical model structure as described above, incorporating the same three major complications associated with diabetes: neuropathy, nephropathy and retinopathy. The overall structures of the models proposed by the DCCT and Eastman et al. are similar to those of a model used to predict retinopathy<sup>50</sup>.

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**Table 13: Complications included within the models**

<b>Complications</b>	<b>Eastman et al.</b> 43,49	<b>Palmer et al.</b> 44	<b>Vijan et al.</b> 46	<b>DCCT</b> 45	<b>Bagust</b> 47
<b>Retinopathy</b>	*	*	*	*	*
<b>Neuropathy</b>	*	*		*	*
<b>Nephropathy</b>	*	*	*	*	*
<b>Heart Disease</b>	*	*		*	*
<b>Stroke</b>		*			*
<b>Hypoglycaemia</b>		*			*
<b>Ketoacidosis</b>		*			
<b>Lactic Acidosis</b>					

\* *Complications included within the model*

The model proposed by Vijan et al.<sup>46</sup> has by far the most limited scope. It calculates the risks of developing blindness and ESRD for patients at different ages of diabetes onset and different levels of glycaemic control. However, the model by Vijan excludes any complication-specific mortality and, therefore, considers only early-stage disease. Furthermore, whilst it is recognised that those patients at high risk of blindness and renal disease (as included in the model) have, in turn, a higher risk of developing neuropathy, Vijan et al. do not include amputation and neuropathy in the model, as a result of an apparent lack of evidence. The model by Vijan calculates the risks of developing blindness and ESRD for patients at different ages of diabetes onset and different levels of glycaemic control.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The data held within these two aspects of the models proposed by Eastman et al. and the DCCT<sup>45</sup> are consistent with the known epidemiology of type 2 diabetes in the US. Despite the DCCT<sup>45</sup> model's difference in focus from that of Eastman et al.<sup>43,49</sup> (from type 2 to type 1 diabetes), the underlying structure appears to be identical, as the complications represented as sub-models are common to both type 1 and type 2 diabetes. The model proposed by Palmer et al.<sup>44</sup> has many similarities to those proposed by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> in terms of underlying model structure, but Palmer et al.<sup>44</sup> and Takeda<sup>29</sup> simulate the disease with markedly wider scope.

The models presented by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> include three complications, a heart disease sub-model and a mortality sub-model, which, together, are believed to reflect the natural history of vascular and neurological complications. Within the models proposed by Eastman et al., the DCCT, Vijan et al., Palmer et al. and Takeda<sup>29</sup> there is no set sequence by which patients may experience the complications included within the model; rather, the sub-models run in parallel. Another element of commonality is that all of the sub-models for each study are assumed to be mutually exclusive, and therefore no compound health states are included in the model.

It can be concluded here that, in terms of model scope, the model proposed by Takeda<sup>29</sup> is at least as comprehensive as the other models identified by the literature search. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## Structure of sub-models

### Neuropathy sub-model

The study by Eastman et al.<sup>43,49</sup> has a major strength in the explicit statements of hazard rates and transition probabilities: this is not included by other authors. Apart from slight disparities in terms of clinical definitions of health states, the DCCT<sup>45</sup> model is identical in structure to that of Eastman et al. In the models proposed by Eastman et al.<sup>43,49</sup> and the DCCT,<sup>45</sup> patients may be in one of three disease states, through which they follow a consecutive progression. The amputation sub-models presented by Palmer et al.<sup>44</sup> and Takeda<sup>29</sup> are largely identical in structure, each including five health states. These are, therefore, similar to the neuropathy structures proposed by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> whereby the patient begins the simulation with no history of amputation. However, the sub-models proposed by Palmer et al.<sup>44</sup> and Takeda<sup>29</sup> also include non-specific mortality.

Within the neuropathy sub-model proposed by Eastman et al.,<sup>43,49</sup> adjustments are made according to ethnicity. Patients enter the sub-model with no neuropathy is present. At the time of clinical diagnosis, the prevalence of significant diabetic neuropathy was approximately 3.5% according to NHANES II in the Eastman et al.<sup>43,49</sup> model. The hazard rate allocated to this event predicted a cumulative incidence for symptomatic neuropathy of 13% eight years after diagnosis, which is reflected in the results of the Rochester Epidemiology Project (REP). The next health state in the sub-model is that of first lower extremity amputation, which was also estimated by the REP. Hazard rates used in the progression to this state are conditional on the duration of diabetes onset. Similarly, hazard rates were calculated from the cumulative incidence of first lower extremity amputation (LEA) and, later, made conditional on the duration of diabetes represented in the model. Subsequent to experiencing a first LEA, patients are at a higher risk of a second LEA.

Palmer et al.<sup>44</sup> suggests that patients with type 1 diabetes are 14 times more at risk of non-traumatic LEA than a non-diabetic population. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The probability of amputation was assumed to decrease by 41% with intensive therapy within the Palmer et al.<sup>44</sup> sub-model. The annual incidence of second LEA is four times higher than that of the first. It is also known that patients have a higher risk of death once the first LEA has occurred.

The model proposed by Vijan et al.<sup>46</sup> does not include a neuropathy sub-model.

## Nephropathy

The epidemiology of type 2 diabetes indicates that 25-50% of patients develop MA.<sup>43,49</sup> The nephropathy sub-model contains four disease states within the DCCT<sup>45</sup> and Eastman et al.<sup>43,49</sup> sub-models. According to these models, patients progress from one state to the next without missing a step. Upon entering the model, patients begin in disease state 'no nephropathy.' Using back-data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a baseline prevalence of MA of 11.5% is assumed within the Eastman et al. sub-model. Adjustments are made again for hazard rates in ethnic minorities.

Patients progress from the initial health state to MA; the respective hazard rate is universal for all durations of disease. This hazard rate is again dependent on ethnicity. The subsequent health state sees the patient progress to proteinuria. The hazard rate for this progression is universal for all durations of diabetes. The progression from proteinuria to ESRD is dependent on the duration of diabetes; the hazard rates for this progression are 0.0042, 0.0385 and 0.074 for durations of 1-11 years, 12-20 years and over 21 years respectively. It should be noted that the clinical definitions for these two states differ amongst the various studies.

It is important to note that the intermediate disease states are referred to differently in the DCCT<sup>45</sup> model and the model presented by Eastman et al.;<sup>43,49</sup> hence the differences between definitions may suggest differences in the internal structures of the sub-models. The nephropathy sub-model proposed by Vijan et al.<sup>46</sup> is largely similar to the model proposed by the DCCT and Eastman et al. yet also includes a non complication-specific mortality state.

The structure of the sub-model described by Palmer et al.<sup>44</sup> differs slightly from those models used by other authors in that they include 10 health states. The four health states included in other sub-models are also included here, yet an additional six health states are also included. From ESRD, the final nephropathy health state in all sub-models previously analysed, the model also includes the treatment of ESRD, e.g. haemodialysis, and includes a health state for ESRD-specific mortality. This represents a significant amount of extra detail included within these models. This suggests a closer reflection of the complication within the models proposed by Palmer et al.<sup>44</sup>.

Clearly the transition probabilities may differ between each of the models proposed by various authors.

## Retinopathy

As with the other sub-models proposed by the DCCT,<sup>45</sup> the retinopathy sub-model is largely identical to that of Eastman et al.<sup>43,49</sup> in terms of structure, despite slightly different clinical definitions of health states. The epidemiology of the disease shows that most people with type 1 diabetes develop non-proliferative retinopathy and 62% develop proliferative retinopathy, so this information was used in the calculation of the transition probabilities within the model presented by the DCCT. The retinopathy sub-model presented by Eastman et al. and the DCCT includes five health states. This is the same for the sub-models proposed by Vijan et al.<sup>46</sup> and Palmer et al.,<sup>44</sup> except that the Macular Oedema (MO) state is omitted and a non-complication-specific mortality state is included. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

There are, however, two different pathways through which patients may progress within the models by Eastman et al. and the DCCT. The hazard rates derived by Eastman et al. for the progression of one state to the next was again obtained from the WESDR. Patients begin in disease state, 'no retinopathy', with the exception of 20% of patients who, at the time of clinical diagnosis of diabetes, were assumed to have background retinopathy. The hazard rate of progression from 'no retinopathy' to 'background retinopathy' is dependent on the duration of the disease in the Eastman et al.<sup>43,49</sup> model.

From the 'background retinopathy' disease state, patients may either progress to the subsequent disease state (proliferative retinopathy) or may progress to significant MO. The hazard rates of progression from proliferative retinopathy to severe vision loss, and from MO to blindness, are conditional on whether or not the patient receives treatment for the disease state. The hazard rates for the progression to either of these states is also conditional on the duration of diabetes. The health state of MO is excluded from the model. Despite the author mentioning this disease state within the literature, no explanation is provided explaining why this important factor is not included within the model. This is clearly a limitation of the model by Eastman et al.<sup>43,49</sup>

Eastman et al. makes adjustments for ethnic minorities who are more at risk of background retinopathy, MO and proliferative retinopathy. As a result of insufficient data, the assumption is made that Asian Americans have the same risk as non-Hispanic white people. The final stage given either pathway is severe vision loss whereby vision is less than 20% of the better eye.

Vijan et al.<sup>46</sup> used data derived from the DCCT<sup>45</sup> in order to establish early rates of progression; these were used as base-case analyses. The incidence and progression of retinopathy were defined as in the DCCT.

## 4.5 OTHER COMPLICATIONS ASSOCIATED WITH DIABETES MELLITUS

The following complications are included only by Palmer et al.<sup>44</sup> and Takeda<sup>29</sup> (with the exception of the inclusion of CVD within the model proposed by Eastman et al.<sup>43,49</sup>). This is an advantage as it results in the model being significantly wider in scope, hence providing a truer representation of the complications encountered by diabetes patients.

### 4.5.1 Heart disease

It should first be noted that Eastman et al.<sup>43,49</sup> do include a CVD sub-model. Within this sub-model the assumption is made that 50% patients have CVD as the disease accounts for 50% of the deaths in patients with diabetes-related ESRD.

Palmer et al.<sup>44</sup> states that, as with the probability of LEA, a patient's probability of developing AMI is dependent on previous heart conditions, demographic and clinical factors. According to Palmer et al., 6-10% of patients having first AMI die immediately, dependent on age and sex. Patients with type 1 diabetes are at two to four times higher risk of developing AMI than the non-diabetic population.

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### 4.5.2 Stroke

The stroke sub-model proposed by Palmer et al.<sup>44</sup> suggests that from having no history of stroke, patients progress to first stroke before moving either to death or to recurrent stroke and then death. At any point in the model, the patient may die of a non-specific mortality. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

Palmer et al.<sup>44</sup> suggest that the known epidemiology of diabetes is that patients are at twice the risk of stroke in comparison with the non-diabetic population. The likelihood of experiencing a stroke is dependent on demographic and clinical factors. Approximately 16% of patients die in hospital.

### 4.5.3 Hypoglycaemia

It is known that hypoglycaemia is common and, ultimately, an important recurrent complication for diabetes patients, yet it is not included in the models proposed by Eastman et al.,<sup>43,49</sup> the DCCT,<sup>45</sup> or Vijan et al.<sup>46</sup> Due to the rapid rate at which the patient experiences the effects of hypoglycaemia, non-complication-specific death is not included in either the sub-model proposed by Palmer et al.<sup>44</sup>. The progression of hypoglycaemia is simple: patients enter the sub-model without having experienced a hypoglycaemic event. Non-serious events are not included in the model. The patient may then progress to experience an event whereby he/she requires medical assistance. From this point, the patient either recovers and reverts back to the initial health state or progresses to the hypoglycaemia-specific death state. The patient cannot remain in the second health state described above as ongoing hypoglycaemia is regarded as fatal. The model by Palmer et al.<sup>44</sup> assumes a case fatality probability of 0.0001.

#### 4.5.4 Ketoacidosis

Ketoacidosis is a complication which is generally specific to type 1 diabetes and is included within the model by Palmer et al.<sup>44</sup> *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### 4.5.4 Lactic Acidosis

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#### 4.5.5 Weight gain

None of the models considered included the potential impact of weight gain on mortality. As discussed in the review of the clinical effectiveness of pioglitazone, pioglitazone has been shown to have a marked and progressive effect in increasing body weight. Whilst the effect of obesity on mortality independent of the effect of lipid concentrations is controversial, there remains the possibility that the increase in body weight due to pioglitazone usage may have an adverse impact on long-term mortality. It is a key shortcoming that these effects are not included in the models.

#### 4.5.6 Mortality

The models by Eastman et al.<sup>43,49</sup> and the DCCT<sup>45</sup> include a separate sub-model which simulates mortality of patients. Each year the mortality model defines whether the individual survives or not. Within the model proposed by Palmer et al.<sup>44</sup>, mortality is not contained within a separate model, but is approached within the various sub-models of complications. It is important to note that the model proposed by Vijan et al.<sup>46</sup> only includes early stage disease and does not include a complication-specific mortality element. Eastman et al.<sup>43,49</sup> uses life tables to obtain the typical life expectancy of a non-diabetic patient; this is then multiplied by a factor of 2.75 to reflect the life expectancy of a patient with type 2 diabetes. The model proposed by the DCCT<sup>45</sup> uses data from the US Department of Vital Statistics in order to obtain typical survival rates. It is not made clear how the model proposed by Palmer et al.<sup>44</sup> apportion rates of mortality.

#### 4.5.7 Cost Aspects

The costs included in each of the models are approached in different ways. The inevitable result of this is a severe difficulty in making close comparisons between the costs used in each of the models. The model by Vijan et al.<sup>46</sup> addresses the risks and benefits associated with improved glycaemic control yet does not directly evaluate costs; the motive behind this is due to costs of decreasing HbA1c levels not being well defined for type 2 diabetes.

The models proposed by the DCCT,<sup>45</sup> Eastman et al.,<sup>43,49</sup> and Palmer et al.<sup>44</sup> include all direct medical costs (for example inpatient and outpatient care, laboratory tests and medical equipment), yet analyse these costs differently. Costs are in 1994 US Dollars, with the exception of Palmer et al.<sup>44</sup> in which they are described in 1996 CHF Francs. Only Eastman et al.<sup>43,49</sup> provide unit costs used. Eastman et al. include costs of screening, treatment and disability costs. The sources of this data were the DCCT<sup>45</sup> study, published literature and Medicare reimbursements.

The model by Palmer et al.<sup>44</sup> includes direct costs and take a third-party payer perspective. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.* Palmer et al.<sup>44</sup> found that the cost driver in the model was the cost of renal failure, which is substantially reduced with the addition of screening for MA and ACE therapy.

**Table 14: Summary costs of implications/events used in the model proposed by Takeda**

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The main costing areas included within the models are the following:

- Screening costs;
- Treatment costs;
- Disability costs.

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On the other hand, Eastman et al. and the DCCT simply stated unit costs and costs per year.

A major issue in the comparison of relevant costs of complications contained within literature is the issue of healthcare setting. Different settings have different implications for healthcare resource intensity and usage. This makes it difficult to define the costs of being in a particular health state. As largely the same sources have been used to derive data within the various models, one would expect the outcomes to be similar, yet evidently this is not the case.

## 4.6 CLINICAL OUTCOMES

The results from the various studies are as follows:

VIJAN ET AL.<sup>46</sup> The primary outcome measure used is lifetime risk. A reduction in HbA1c levels from 9%-7% for patients with onset before 50 years of age results in a 2.3% point decrease in lifetime risk of blindness due to retinopathy. A decrease from 11%-9% in a patient with onset

before 50 years of age results in a 5.3% decrease in blindness risk. The same relationship holds for the ESRD sub-model. The conclusions drawn are that substantially greater effectiveness is achieved in moving from poor to moderate glycaemic control than from moderate to normal control.

PALMER ET AL:<sup>44</sup> The primary outcome measures used in this study are mean total lifetime costs per patient, mean life expectancy, and cost-effectiveness (measured in terms of costs per LYG). Intensive therapy increased life years gained but also increased total lifetime costs.

DCCT<sup>45</sup> STUDY: The primary outcome measure used is LYGs, but the study also tracked sight years, ESRD-free years, amputation-free years, and QALYs. QALY values were 0.69 for blindness, 0.61 for ESRD (Lawrence), 0.8 for LEA, 0 for death and 1 for all other health states. The incremental cost per LYG was found to be US\$28,661.

EASTMAN ET AL:<sup>43,49</sup> The primary outcome used is incremental cost per QALY. The incremental cost per QALY of intensive treatment over conventional is US\$16,002. This study uses the same utility outcomes as those used in the DCCT<sup>93</sup> study, derived from largely the same sources. Maintaining an HbA1c value of 7.2% is predicted to reduce the cumulative incidence of blindness, ESRD and LEA by 72%, 87% and 67% respectively. Total estimated life expectancy is increased by 1.39 years.

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Whilst each of the models present their findings in different formats, they all track the average increase in life expectancy from conventional to intensive therapy, with the exception of that proposed by the DCCT.<sup>45</sup> Despite this homogeneity, there are clearly differences between the findings due to the differences in the ages of diabetes onset and also the type of disease. It is likely that the increase in average life expectancy is higher for treatment of type 1 diabetes as the onset of the disease is earlier and hence the competing risks are less. Another major impact is in the definition of comparator therapies. The earlier studies focus on the comparison of intensive glucose control therapies with non intensive therapies. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The average life expectancies are shown in Table 15, as tabulated below.

**Table 15: Average increases in life expectancy as described by the studies**

Author	Outcome Measure	Resulting Increase as a Result of Intensive Therapy	Target of Intensive Glycaemic Therapy	Comments
Vijan et al.	Average increase in life expectancy	1.3 years	2% decrease in HbA1c level (actual start level not specified)	Age at onset = 45 years
DCCT	Mean years free from first significant complication	15.3 years	N/a	None stated
Eastman et al.	Average increase in life expectancy	3 years	A decrease of 2.8% in HbA1c level (from 10% to 7.2%)	Assumes non-CVD mortality amongst diabetic population
Palmer et al.	Average increase in life expectancy	7.4 years	Not stated	Risk of AMI and Stroke reduced by 41% Conventional Vs. Screening + Intensive

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#### 4.6.1 Utility Scores

There has been considerable debate on the issue of utility scores for patients with diabetes. Of the four studies evaluated, only the DCCT<sup>45</sup> study and Eastman et al.<sup>43,49</sup> make an attempt to apportion quality of life scores to end-stage complications associated with type 2 diabetes. Both studies use identical scores for the end-stage diseases. This reflects the paucity of data in this area as both studies use the same source, rather than a high level of certainty in the values used. The study by the DCCT<sup>45</sup> makes the assumption that, as compound health states are not incorporated in the model, where patients reach the end stage in two or more of the complications, they assume the lower utility of the complications which they have experienced. For example, where a patient reaches blindness and LEA, the quality of life score used is 0.61, the score for blindness. This implies that the models are likely to underestimate the quality of life impact for an individual, as patients who are blind and have had an amputation would clearly

prefer not to be blind; there should be a difference in quality of life between these two scenarios. A suggested (and more realistic) alternative would be to multiply the two utility scores, so, for example, in the compound health state described above the resulting utility score would be  $0.80 \times 0.69 = 0.552$ .

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#### **4.6.2 Validation of the Takeda model<sup>29</sup>**

**Table 16: Comparison of incidence estimates for the model against UKPDS data**

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#### **4.6.3 Assumptions made within the Takeda model<sup>29</sup>**

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#### **4.6.4 Conclusions on the critical appraisal of the Takeda model<sup>29</sup>**

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### **4.7 KEY ECONOMIC RESULTS FOR PIOGLITAZONE**

**Table 17: Baseline cost per LYG for pioglitazone**

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#### **4.7.1 Impact of structural assumptions within the model**

**Table 18: Economic impact of assumptions within the Takeda model**

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#### **4.7.2 Conclusions on the health economics of treatment with pioglitazone in type 2 diabetes**

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## **4.8 ROSIGLITAZONE**

### **4.8.1 Results of Systematic Search for Economic Studies of Rosiglitazone**

There are no published studies investigating the health economics of rosiglitazone or, indeed, of any other thiazolidinedione (TZD). The only available economic evidence concerning rosiglitazone is that obtained as part of the confidential submission by the sponsoring body, GlaxoSmithKline (GSK).<sup>28</sup> This confidential economic submission is based closely upon a published economic model by Bagust et al.<sup>47</sup>

### **4.8.2 Critical Appraisal of The Economic Submission for Rosiglitazone**

A structured proforma has been used in the critical appraisal of the economic submission for rosiglitazone.<sup>48</sup> A detailed discussion of some of the key factors is given below.

#### **4.8.2.1 The GSK Cost-effectiveness model**

The model provided by GSK has two sub-models, a metabolic model and an economic model. The metabolic model uses treatment-specific values for insulin sensitivity and beta cell function to predict Fasting Plasma Glucose (FPG), which is then converted into HbA1c. The economic model then uses the predicted value of HbA1c to estimate the future incidence of long-term complications and mortality for different treatment strategies.

These two models are linked together. In particular, the metabolic model represents the natural inter-relationship of clinical metabolic variables and their normal progression in type 2 diabetes. The basic variables that drive this model are insulin sensitivity and beta-cell function. The metabolic model provides the progression of glucose levels (measured in HbA1c) through time for each one of the available treatment pathways followed. In addition, it presents the progression of other secondary clinical variables, such as body mass index, blood pressure, triglycerides and cholesterol. The outputs of the metabolic model are then used as inputs to the economic model. The HbA1c levels mainly contribute to the calculation of micro-vascular complications in the economic model. The values of Systolic Blood Pressure and of the ratio Total Cholesterol/HDL Cholesterol are averaged per age group and are used in the economic model, in order to estimate the cardio-vascular disease death rates. The economic model is a Markov model for the long-term type 2 complications of newly diagnosed patients. Data from well-attested published models, as well as very recent clinical results are employed to estimate mortality rates, transition probabilities and number of patients in each state of the major complications of type 2 diabetes. Moreover, the model includes a very detailed module for the calculation of health care costs. Its main outputs are cumulative QALYs, life-years and health costs by time from diagnosis and lifetime health care costs.

### 2.8.2.2 Statement of the problem

The submission<sup>28</sup> contains a clear statement of the problem, that is to perform a cost utility analysis of adding rosiglitazone to sulphonylurea or metformin compared with other combination therapies or changing to insulin.

GSK supports that there is strong clinical and economic evidence available for the effectiveness and toleration of rosiglitazone in the treatment of type 2 diabetes patients. Moreover, the company believes that there is significant ambiguity in the existing NICE guidance with respect to the positioning of rosiglitazone in the treatment pathway of type 2 diabetes.

Thus, GSK suggests that the Institute should carefully consider the following aspects when reviewing the current guidance for Avandia:

- Patients with inadequate blood glucose control on metformin, who are obese, should be considered for rosiglitazone combination therapy, as an alternative to sulphonylurea.
- Patients with inadequate blood glucose control on sulphonylurea, who are unable to take metformin, should be considered for rosiglitazone combination therapy.
- Patients treated with an established metformin and sulphonylurea combination should not subsequently be offered a switch from one of these components to glitazone therapy.

The population of interest in the study is defined as those people with type 2 diabetes whose blood glucose levels are poorly controlled with oral monotherapy with either metformin or sulphonylureas.

The study focuses on the possible lifetime clinical and economic outcomes. The key economic results are reported in terms of the cost per quality adjusted life year.

The perspective of the analysis is on direct medical costs with a specific focus on the UK NHS costs.

Clinical benefits are discounted at 1.5%, costs are discounted at 6%.

## 4.9 THE GSK METABOLIC SUB-MODEL

### 4.9.1 General Description

The metabolic model represents the natural inter-relationships of clinical metabolic variables and the normal progression of these variables over time in type 2 diabetes patients. The following figure illustrates the relationships between key variables of the metabolic model:

#### **Diagram 1: Interrelations of metabolic variables**

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#### 4.9.2 Main Output of Metabolic Model: HbA1c Progression

The main output of the metabolic model is the level of glycaemia (HbA1c) during all years after diagnosis if a specific treatment pathway is followed. The diagram below and the description that follows explain the methods employed to derive the HbA1c values for each treatment pathway:

#### Diagram 2: Description of the progression of glucose levels in the metabolic model

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#### 4.9.3 Secondary Outputs of Metabolic Model: Weight, Blood Pressure and Lipids Progression

In addition to the glycaemic progression in type 2 diabetes, the metabolic model provides estimates also for other inter-related clinical variables.

Using information for males and females with diabetes, separate regression models were developed from the NHANES3 data set<sup>28</sup> to predict each one of the following clinical variables:

- *Body Mass Index (BMI)*
- *Systolic Blood Pressure (SBP)*
- *Diastolic Blood Pressure (DBP)*
- *Total Cholesterol (TC)*
- *LDL Cholesterol (LDL-C)*
- *Triglycerides (TG)*
- *HDL Cholesterol (HDL-C)*

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#### 4.9.4 Calibration of Metabolic Model: Treatment Effects

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In order to estimate the effect that each treatment or combination of treatments has on insulin sensitivity and beta cell capacity, GSK has used data from the following sources:

- UKPDS results
- Published papers detailing trials
- Unpublished SKB trial reports.

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**Table 19: Additive and multiplicative effects of the different regimens on the metabolic variables**

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#### 4.9.5 Parameter Values and Assumptions

The underlying population profile assumes 1,000 patients, newly diagnosed with Type II diabetes, based on the numbers expected from a population structure equivalent to the European Standard population.

The insulin sensitivity and beta cell function at diagnosis are assumed to be the same for males and females.

The user can choose the percentage of people in each ethnic group. In the central estimate, the population consists of 100% white people. This proportion is not representative of the British population. However, the company has been conservative in this assumption, as it has assumed only white people, who have lower risk of progressing to micro-vascular states compared to black people.

The assumptions made for the rest of the key parameter values are presented in the following table:

**Table 20: Key parameter values in the GSK model**

Parameter Values	Males	Females
BMI age offset	5	10
BMI peak offset	-0.7	-1
BMI excess for new diabetics	1	1
Initial carbohydrate intake: Diabetics	1.43	1.43
Insulin: BMI conversion factor	0.08	0.08
BMI: Sensitivity conversion factor	0.035	0.035
Carbohydrate: BMI conversion factor	0.3	0.3
Carbohydrate: Plasma glucose conversion factor	0.5	0.5
Baseline output calibration adjustment for BMI: Diabetics	5	1

No source was provided from GSK for any of the above figures.

The prevalence of smoking for each age group of diabetic males and female is taken from Eastman's model<sup>43,49</sup> and is presented in the following table:

**Table 21: Prevalence of smoking**

Age Group	Diabetic Males	Diabetic Females
<25-44	40.70%	25.30%
45-64	27.00%	22.00%
65-90+	13.20%	11.8%

We have looked at Eastman’s paper and found out that the prevalence values are for U.S. people with diabetes and are taken from Cowie CC and Fujimoto WY.<sup>59,60</sup>

The initial conditions (baselines) for the body mass index, the insulin sensitivity and the effective beta-cell function are defined as follows:

- The body mass index (BMI) is assumed 25 for lean patients and 31 for overweight patients.
- The insulin sensitivity level (HOMA % S) is set to 40 for lean patients and 30 for overweight patients.
- The beta-cell function level (HOMA % B) is set to 40 for lean patients and 50 for overweight patients.

#### 4.9.7 Therapy Scenarios

The scenarios examined in the model are the following:

**Table 22: Treatment pathways**

SCENARIO:	Weight	Step 1	Step 2	Step 3	Step 4	Step 5
1	Normal	D & E	S	S + M	I	
2	Obese	D & E	M	M + S	I	
3	Normal	D & E	S	S + M	S + R(4mg)	I
4	Obese	D & E	M	M + S	M + R(4mg)	I
5	Obese	D & E	M	M + S	S + R(4mg)	I
6	Normal	D & E	S	S + R(4mg)	I	
7	Obese	D & E	M	M + R(4mg)	I	
8	Obese	D & E	M	I		
9	Normal	D & E	S	I		
10	Obese	D & E	M	M + S	M + R(8mg)	I
11	Obese	D & E	M	M + R(8mg)	I	
12	Obese	D & E	S	S + R(4mg)	I	
13	Obese	D & E	S	I		

The model only allows patients to receive one of the four following types of therapy during any half-yearly time period:

- diet & exercise
- monotherapy OHA
- combination OHA or
- Insulin-based therapy

The switching threshold between treatments is fixed for each scenario, rather than being dependent on the treatment that patients receive. The threshold has been set to: FPG = 9.3 mmol/l (equivalent to HbA1c=7.5%, using the developed regression model).

There is some consensus that the threshold used by clinicians to change treatments is dependent on the efficacy of the specific treatment. Thus, the threshold used in practice is not the same for all the types of treatment (drugs).

We have performed sensitivity analysis on the switching threshold of HbA1c (see later section in this report). However, we could not apply a different threshold for each treatment, as the model allows only one switching threshold, which remains constant for all the drugs in the treatment pathway.

#### 4.9.7 Drug and Treatment Costs

It is assumed that patients receive fixed dosage and that no drug titration takes place. Moreover, there is a fixed cost for dispensing each prescription.

The *daily drug costs* that are used in the model are presented in the following table:

**Table 23: Daily drug costs**

<b>Drug:</b>	<b>Tablet Size</b>	<b>No per day</b>	<b>Daily Cost</b>
Glibenclamide	2.5 mg	4	£0.1371
Metformin	850 mg	3	£0.1114
Avandia	4 mg	1	£0.9500
Avandia (max.dose 8mg)	4 mg	2	£1.9000
Insulin	20 IU	3	£0.9000
Needles for Insulin		3	£0.0800

These costs were derived from the British National Formulary 42.<sup>61</sup> The drug costs used in the submission model are identical to the ones reported in BNF 42.

The total *annual treatment costs* are calculated, which, according to the regimen followed, include:

- **urine testing costs (only for insulin treated patients)**

The annual cost is £64. The model assumes 4 contacts per annum of specialist advice.

- **glucose testing costs (consumables)**

The annual cost is £34.31 for all the regimens, except for insulin treatment that it is £102.94.

- **prescribing costs (drugs and dispensing)**

The annual cost for drugs is calculated using the prices provided in the previous table. The annual cost for dispensing is £3.90 (4\*0.975) for all the regimens, except for insulin treatment that it is £5.85 (6\*0.975).

No source was provided in the GSK submission concerning the treatment costs.

The *total annual cost* for each treatment is calculated using the above data for the drug and treatment costs:

**Table 24: Annual treatment cost for each drug**

Treatment	Cost
D & E	£34.31
S	£88.30
M	£78.91
R (4mg)	£366.10
R (8mg)	£732.19
I	£611.17

#### 4.9.8 Long-term Progression of Glycaemia (HbA1c)

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### Diagram 3: Relationship between IS/Beta cell and HbA1c as seen in the metabolic model

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### 4.9.9 Belfast Diet Study

The Belfast Diet Study<sup>58</sup> is a 10-year prospective natural history study of 432 newly diagnosed diabetic patients aged 40-69 years, which was undertaken to assess the effect of intensive dietary management. The results of the study demonstrate that patients continuing on diet alone for the first 10 years after diagnosis have a small but progressive rise in FPG, which is associated with an equally progressive fall in beta-cell function, but not with a change in either obesity or insulin sensitivity. GSK's model is in accordance with these results.

Furthermore, the Belfast study indicated that failure of diet therapy within the first 10 years is related to higher rates of glucose rise and beta-cell decline. This failure occurs earlier in patients with higher initial glucose concentration, lower initial beta-cell function, lower age and, for subjects maintained on diet therapy alone for at least 6 months, greater obesity.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### 4.9.10 Regression model: $HbA1c = f(FPG)$

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## **Table 25: Diagnostics for the regression model: $HbA1c=f(FPG)$**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

### **4.9.11 HOMA/CIGMA models and Progression of Glycaemia:**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

### **4.9.12 Output Risk Factor Variables**

As mentioned earlier, population data from NHANES3<sup>28</sup> were used to describe the relationship between risk factors and other demographic and metabolic variables. The regression models developed from the NHANES3 data set are used to estimate the levels of the following variables for each age group and for each time slot after diagnosis:

- Body Mass Index (BMI) (This variable is additionally updated in the subsequent periods in line with the central BMI trajectory, which reflects changes in plasma insulin levels, calorific intake and direct treatment effect on weight).
- Systolic Blood Pressure (SBP)
- Diastolic Blood Pressure (DBP)
- Total Cholesterol (TC)
- LDL Cholesterol (LDL-C)
- Triglycerides (TG)
- HDL Cholesterol (HDL-C)

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

However, diagnostics and accuracy measures were not provided from the company concerning the models described above. Therefore, we have not been able to validate those models.

## **4.10 THE GSK ECONOMIC SUB-MODEL**

A deterministic Markov model was used for the long-term type 2 diabetes complications of newly diagnosed patients. The model consists of a network of classical inter-connected Markov chain modules, which all reconcile to a central survival module. It projects the natural progression of type 2 diabetes over time, in order to assess lifetime costs and complications and it is a cohort study. Various anti-diabetic agents can be introduced individually or in combination. Well-attested probabilities were used from epidemiological and clinical sources to estimate the proportions of patients likely to suffer from a range of common complications of diabetes over their remaining lifetime.

#### 4.10.1 Cohort information

The cohort used in the model is described in Table 26.

**Table 26 Cohort information used within the published models**

Author	Disease Type	Cohort Age Range (years)	Source of Cohort Information	No. of Patients in Cohort
GSK model <sup>28</sup>	Type 2	57 (mean)	UKPDS	1000

#### 4.10.2 Inputs

The basic parameters used in the model are the following:

*Distribution of new patients developing type II diabetes by age and sex:*

- 40.97% males and 59.03% females
- Average age: 56.50 for males and 57.81 for females

These are used throughout the model as the patients alive at the outset.

*Relative mortality multipliers for nephropathy, neuropathy, retinopathy, CVD/CHD and stroke states:* The default values were determined interactively to reproduce prevalence and mortality figures in published literature. The micro-vascular multipliers were derived from a variance-minimisation heuristic to reconcile the overall mortality at each age in the mortality module with the implied mortality calculated for each complication module. The macro-vascular multipliers were generated by a process of iterative re-calibration.

*Distribution of new patients in each state by condition, age and sex:* These are used to calculate the progression of patient cohorts in each state in the model. The proportions are the ones used in Eastman's model.<sup>45,49</sup>

The baseline prevalence values included in the GSK model are identical to the ones used by Eastman.

*Proportion of patients in each ethnic group.* The model assumes 100% white patients. This is not representative of the British population.

*Relative risk multipliers per ethnic group in developing each condition:* These are taken from Eastman's model and are used to adjust the transition probabilities in each disease state.

The risk multipliers are taken from Tull ES, Roseman JM, Ghodes D, Stern MP and Mitchell BD<sup>62,63,64</sup> and are used also by Eastman in the development of model of complications for type 2 diabetes.

*Glycaemic levels:*

Standard HbA1c (DCCT) = 10.00

Average HbA1c at Diagnosis = 7.00

These are used to calculate the Eastman power function and the WESDR linear threshold used in the estimation of the transition probabilities.

The HbA1c level for standard care used in the GSK model is identical to the one provided from DCCT.

*Glycaemic control parameters:* These are the parameters for the Eastman power functions and WESDR linear functions. They are used to modify the rates of progression to the several morbid states according to changes in glycaemic control.

The glycaemic control parameters that are included in the GSK model are identical to the ones used by Eastman.

*Choice of glycaemic gradient:* The user can choose the gradient model (Eastman power function or WESDR linear threshold) to be used for the progression of micro-vascular complications. The WESDR linear threshold is employed in the central estimate in the submitted model.

*Annual discounting rates:*

Cost rate = 6.00%

Outcome rate = 1.50%

These factors are calculated for each of the time periods throughout the model.

The method employed is examined and considered appropriate.

*Discounting offset from date of diagnosis:* This factor specifies the number of years after which the discounting should start and is used when comparisons between scenarios only diverge after a fixed period. In the model, the factor is assumed to be zero, which means that the discounting starts from the first period.

*Cohort size:* The total size of the annual diagnosis cohort is assumed to be 1,000.

*Choice of CVD models:* The user can choose the CVD risk model (Framingham<sup>65</sup> or UKPDS<sup>66</sup>) to be used in the estimation of CVD event rates and mortality. The UKPDS-based risk equations are employed for the central estimate in the submitted model.

The following are taken into account by the model, only when the Framingham risk equations are used to estimate cardio-vascular events and death rates:

*Relative reduction in CVD mortality rates from reduced HbA1c for conventional and intensive treatment:* These are used to calculate the combined mortality rates. The source for these is UKPDS 33.

**Table 27: CVD mortality reduction from reduced glucose**

Glycaemia			
Regime	FPG Limit	HbA1c Limit	Mortality Reduction
Conventional	15.0	9.25	
Tight Control	6.0	5.90	-7.10%
Target	9.3		-4.50%

*Reduction in SBP and relative reduction in CVD mortality for conventional treatment and tight control:* These are used to calculate the combined mortality rates. The source for these is UKPDS 38.

**Table 28: CVD mortality reduction from reduced SBP**

Systolic Blood Pressure		
Regime	Mean	Mortality Reduction
Conventional	154	
Tight Control	144	-28.70%
Target	154	0.00%

*Reduction in triglycerides & relative reduction in CVD mortality for conventional treatment and tight control:* The source for these is VA-HIT study.

**Table 29: CVD mortality reduction from reduced triglycerides**

Triglycerides		
Regime	Mean	Mortality Reduction
Conventional	1.82	
Tight Control	1.30	-22.00%
Target	1.87	0.00%

#### 4.10.3 Variables transferred from the Metabolic model

##### *HbA1c*

The following estimates concerning HbA1c levels are transferred from the metabolic model:

- Mean HbA1c levels at 6-month intervals
- Regimen applicable to treatment in each 6 month period (Diet & Exercise, Oral Monotherapy, Oral Combination therapy, Insulin-based therapy)
- Average HbA1c in 5 year periods
- Average proportions of patients on each of the therapies in 5-year periods. These are used to calculate the cost of diabetes.

- Mean HbA1c for micro-vascular (nephropathy, neuropathy and retinopathy) model periods. These are used in calculations in the respective micro-vascular sub-models.
- Average annual treatment cost corresponding to the specific treatment used in each 6-month period.

These figures provide estimates for mean HbA1c, which are used in the economic model, especially in the micro-vascular complication modules.

#### *Body Mass Index – Blood Pressure - Lipids*

Mean values for the body mass index, blood pressure and lipids are provided from the Metabolic model. These are then used to drive the cardio-vascular disease risk relationships in this model.

Mean values of the following for each sub-cohort by age (per 6 months) and sex are transferred from the metabolic model:

- Body Mass Index (BMI)
- Systolic Blood Pressure (SBP)
- Diastolic Blood Pressure (DBP)
- Triglycerides
- HDL-Cholesterol
- Total-Cholesterol
- LDL-Cholesterol

The Systolic Blood Pressure and the ratio of Total Cholesterol over HDL cholesterol are then averaged per 5-year age-group and they are used to drive the cardio-vascular disease risk relationships for patients with type 2 diabetes.

#### **4.10.4 Model structure and scope**

The economic component of the GSK model is based closely upon a published economic model by Bagust et al.<sup>47</sup>

**Table 30: Types of modelling used by the studies**

<b>Author</b>	<b>Type of Simulation</b>	<b>Type of Model</b>	<b>Decision Analysis</b>	<b>Monte-Carlo</b>
<b>GSK model</b>	None	Markov	Yes	No

The model by Bagust<sup>47</sup> projects the natural progression of type 2 diabetes over time, in order to assess lifetime costs and co-morbidities. The model incorporates the major complications associated with diabetes: cardiovascular disease, neuropathy, nephropathy, retinopathy and hypoglycaemia.

Within the model proposed by Bagust, complications are presented as sub-models, linked to the consequences of CVD and a mortality sub-model, which, as a whole, forms the overall structure of the model.

It can be concluded here that, in terms of model scope, the model proposed by Bagust is at least as comprehensive as the other models identified by the literature search. Through incorporating seven complications, CVD, and a complication-specific mortality element within each relevant sub-model, the underlying structure of the model provides a broad representation of the complications a type 2 diabetes patient may experience.

The overall structure of the model included in the GSK submission is identical to the published model by Bagust. A deterministic Markov model was used for the long-term type 2 diabetes complications of newly diagnosed patients. The model consists of a network of classical inter-connected Markov chain modules, which all reconcile to a central survival module. It projects the natural progression of type 2 diabetes over time, in order to assess lifetime costs and complications and it is a cohort study. Various anti-diabetic agents can be introduced individually or in combination. Well-attested probabilities were used from epidemiological and clinical sources to estimate the proportions of patients likely to suffer from a range of common complications of diabetes over their remaining lifetime.

#### **4.10.5 Structure of sub-models**

##### **4.10.5.1 CVD, CHD and Stroke Models**

The Bagust model uses Framingham multi-variate risk model to estimate cardiovascular morbidity and mortality. The model estimates the prevalence of all cardio-vascular disease, coronary heart disease and history of stroke. Mortality rates due to cardiovascular causes were estimated using the Framingham equation. The cardiovascular disease sub-model in the GSK model is identical in structure to the published Bagust model.

##### **4.10.5.2 UKPDS Risk Equations**

The UKPDS risk equation for CHD is implemented in the model as published in UKPDS 56.<sup>66</sup> The UKPDS effects on mortality are introduced as risk adjustments in the estimation of cardiovascular deaths, in order to reflect the benefit that tight control of hypertension and hyperglycaemia has in extended life. In order to integrate with the rest of the model, corresponding risk factors are estimated for CVD and Stroke risks, based on scaling Framingham risk estimates for these conditions by factors dependent on the ratio between UKPDS and Framingham risk estimates for CHD.

It is assumed that the UKPDS risk evaluation can be applied incrementally to time periods after diagnosis using current risk factor values. Moreover, CHD and stroke risks estimated by Framingham equations are assumed to increase in UKPDS in a similar manner to CHD risks.

The UKPDS 56<sup>66</sup> model coefficients are provided in the model. These are presented in the following table:

**Table 31: UKPDS 56 model coefficients**

Parameter	Risk Ratios for:	Estimate
q0	Intercept	0.0112
β1	one year of age at diagnosis	1.059
β2	female sex	0.525
β3	Afro-Caribbean ethnicity	0.39
β4	Smoking	1.35
β5	1% increase in HbA1c	1.183
β6	10mmHg increase in SBP	1.088
β7	unit increase in logarithm of lipid ratio	3.845
d	each year increase in duration	1.078

Common factor values for males and females are calculated using the model coefficients, in order to simplify later calculations (males: 0.000005 and females: 0.000003). The values of the UKPDS 56 intermediate variable (q) are then calculated for males and females for each sub-cohort at diagnosis and at 5-year age points. The parametric model employed is the following:

$$q = q_0 \beta_1^{age-55} \beta_2^{sex} \beta_3^{ac} \beta_4^{smok} \beta_5^{h-6.72} \beta_6^{(sbp-135.7)/10} \beta_7^{\ln(lr)-1.59}$$

Thus, the probability (risk) of a CHD event over t years in a patient who has had diabetes for T years is then estimated using the previous q calculations and the following formula:

$$R_T(t) = 1 - \exp\left\{-qd^T \left(\frac{1-d^t}{1-d}\right)\right\}$$

The above methods are employed and thus the model provides estimates for the following 2.5/5 year period CHD risks for males and females for each sub-cohort. These estimates are then combined with the Framingham<sup>65</sup> risk estimates in the model to derive CVD and Stroke risks as well as mortality rates for the following 2.5/5 year period for males and females for each sub-cohort.

Summarising, the model estimates the following 2.5/5 year period risks for males and females for each sub-cohort:

- CHD risks: UKPDS
- CVD risks: Estimated UKPDS
- Stroke risks: Estimated UKPDS
- CVD annual mortality rate: Estimated UKPDS
- CHD risk ratios: UKPDS/Framingham (these figures are descriptive only)

#### 4.10.5.3 UKPDS 56

The UKPDS 56 study<sup>66</sup> provided a parametric model for predicting the risk of new CHD events in patients with type 2 diabetes. Unlike previously published models, the risk equation derived

from this study has been specifically designed for people with type 2 diabetes, comes from a very big population and includes glycaemia, systolic blood pressure and lipid levels as risk factors, in addition to age, sex, ethnic group, smoking status and time since diagnosis.

The UKPDS risk equation for CHD events is correctly employed in the model included in the GSK submission. In particular, the parameter estimates are identical to the UKPDS ones, the common factors are properly generated and the equation and risks are correctly calculated.

#### 4.10.5.4 Framingham Risk Equations

The Framingham multivariate risk models are employed, in order to calculate the death rates and the number of new cases of CHD, CVD and Stroke in each model period and surviving cohort. Moreover, the number of new cases of CHD, CVD and Stroke are estimated using also the UKPDS-based equations, in order to reflect the benefit that tight control of hyperglycaemia (not included in Framingham models) has in extended life. The UKPDS equations are used for the central estimate in the submitted model.

The estimates of events are calculated using multivariate models. Definitions of MI, stroke, CHD and CVD are those employed in the formulation of the Framingham risk equations.

The Framingham<sup>65</sup> model coefficients are provided in the model. These are presented in the following table:

**Table 32: Framingham model coefficients**

Factor	CVD death	Stroke	MI	CHD event	CHD death	CVD event
Beta 0	-5.0385	26.5116	11.4712	15.5305	11.2889	18.8144
Female	0.2243	0.2019	10.5109	28.4441	0.2332	-1.2460
ln(Age)	8.2370	-2.3741	-0.7965	-1.4792	-0.9440	-1.8443
ln(Age)^2	-1.2109	0.0000	0.0000	0.0000	0.0000	0.0000
ln(Age) [Fem. only]	0.0000	0.0000	-5.4216	-14.4588	0.0000	0.3668
ln(Age)^2 [Fem. only]	0.0000	0.0000	0.7101	1.8515	0.0000	0.0000
ln(SBP)	-0.8383	-2.4643	-0.6623	-0.9119	-0.5880	-1.4032
Smoking	-0.1618	-0.3914	-0.2675	-0.2767	-0.1367	-0.3899
ln(Chol/HDL)	-0.3493	-0.0229	-0.4277	-0.7181	-0.3448	-0.5390
Diabetic	-0.0833	-0.3087	-0.1534	-0.1759	-0.0474	-0.3036
Diabetic & Fem.	-0.2067	-0.2627	-0.1165	-0.1999	-0.2233	-0.1697
LVH	-0.2946	-0.2355	0.0000	-0.5865	-0.1237	-0.3362
LVH [Males only]	0.0000	0.0000	-0.1588	0.0000	0.0000	0.0000
Theta 0	0.8207	-0.4312	3.4064	0.9145	2.9851	0.6536
Theta 1	-0.4346	0.0000	-0.8584	-0.2784	-0.9142	-0.2402

The mean systolic blood pressure, the prevalence of smoking, the total/HDL cholesterol ratio, the proportion with ECG-LVH, the age and sex are employed to calculate the intermediate multi-factors in the 6 Framingham risk equations for each age-group of the model. These are assumed to be a linear function of the risk factors:

$$\mu = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k$$

The macro-vascular events examined are the following:

- CVD event
- CVD death
- Stroke
- MI
- CHD event
- CHD death

The calculated factors ( $\mu$ ) are then used to calculate the death rates and number of new cases of CHD, CVD and Stroke in each model period by age, sex and sub-cohort. In particular, CVD death rates are estimated using the Framingham equation:

$$P(T > t) = 1 - \exp\left(-\exp\left(\frac{\ln(t) - \mu}{\sigma}\right)\right)$$

where: T: time until the event of interest and

$\ln(\sigma) = \vartheta + \vartheta_1 \mu$  is considered to be a linear function of  $\mu$ .

These rates are later employed in the model to calculate the mortality rates. Moreover, the proportion of new cases of CVD, CHD and Stroke developed in previous 2.5/5 year period are estimated using the same model.

The user can choose between two CVD models. In particular, either the Framingham equations or the UKPDS-based equations can be used to estimate the macro-vascular disease event rates. Thus, the proportion of new cases of CVD, CHD and Stroke developed in the previous 5-year period are estimated using also the UKPDS multi-variate risk equation. The model included in the GSK submission uses the UKPDS-based equations. It should be noted that Framingham equations are always used for non-diabetic CVD, CHD and Stroke risks, as UKPDS estimates are only relevant to patients with type 2 diabetes.

#### **4.10.5.5. Framingham Heart Study**

The Framingham Heart Study<sup>65</sup> provided equations to predict risk for the following cardiovascular disease end-points: MI, CHD, death from CHD, stroke, cardio-vascular disease and death from cardio-vascular disease. These equations are based on measurements of several known risk factors and have indicated that a multi-factor approach, one that takes into account all the risk factors, is probably the best strategy for the prevention of coronary heart disease. The parametric model used in this study is considered to have significant advantages, as it provides

predictions for different lengths of time and its probabilities can be expressed in a straightforward way.

The Framingham risk equations for cardio-vascular events are correctly employed in the model included in the GSK submission. In particular, the parameter estimates are identical to the Framingham ones, the parametric model is properly applied and the death rates and number of new cases are correctly calculated. Prevalence rates of CVD, CHD and Stroke are calculated for males and females by age. These are later employed to estimate the inpatient costs in the model.

#### **4.10.6 Mortality**

Within the models proposed by Bagust and GSK, mortality is contained within a separate sub-model model. The various components of the mortality module are combined and analysed by age, sex, and macro-vascular status for the different sub-cohorts. Thus the combined mortality rate for diabetics is estimated.

“CVD mortality” is based on Framingham (for non-diabetics) and UKPDS (for diabetics) risk equations, whereas “other mortality” is derived from OPCS mortality statistics in U.K combined with Prevalence of Diagnosed Diabetes from Diabetes in America. Moreover, the UKPDS effects on mortality are introduced as risk adjustments in the estimation of cardio-vascular deaths, in order to reflect the benefit that tight control of hypertension and hyperglycaemia has in extended life. The estimated mortality components are combined with relative risk multipliers for each macro-vascular status, in order to generate the “combined mortality rates” for diabetics without CVD, with CVD, CHD and Stroke. Finally the “revised annual death rates” are rates that are calculated by micro-vascular complication state module, based on mortality multipliers relative to non-diabetic mortality rates.

The morbidity components for the various diabetic causes are estimated combining data from two sources:

- OPCS Mortality by Cause Statistics 1995 (used to determine rates for males and females for all causes, CVD and Non CVD)
- Prevalence of Diagnosed Diabetes from Diabetes in America (2<sup>nd</sup> edition)

The following annual death rates are calculated:

- Annual death rates for diabetics from Non-CVD cases adjusted for under-recording by age and sex.
- Annual death rates from Non-CVD cases in diabetes adjusted for independence (competing risks) by age and sex.
- Annual death rates for the major complication sub-groups by age and sex: diabetes & renal, diabetes & neuro/PVD and other diabetes causes.
- Annual CVD death rates by age-group and sex.

These are estimated for the non-diabetic population using the Framingham risk equations<sup>65</sup> and for the diabetic population using the UKPDS-based risk equations.<sup>66</sup>

- Annual CVD death rates by age group, sex and sub-cohort.

These death rates are adjusted for tighter glycaemic, hypertensive and triglyceride control only when the Framingham CVD models are used. The glycaemic and hypertensive adjustment

reflects the UKPDS “tight glycaemic / blood pressure control” regimen. The triglyceride adjustment is based on the results of the VA-HIT trial when triglyceride levels are reduced. All the above modifications are later used in the model to calculate the *combined mortality rates*.

- Annual death rates by ethnic group for diabetics with ESRD.

The default values are the ones used by Eastman. A weighted average of death rates per age group is provided according to the percentage of people in each ethnic group. The proportion of ESRD deaths due to CVD is assumed to be 50% (This percentage is identical to the one used by Eastman<sup>43,49</sup>).

The various components of mortality are combined and analysed by age, sex macro-vascular status and sub-cohort. Thus, the *combined mortality rates* for diabetics are estimated. These are mortality rates for diabetics “without CVD”, “with CVD”, “with CHD” and “with Stroke”. All of these rates are the result of combination of previous mortality estimations and the last three are additionally adjusted by mortality multipliers for CVD, CHD and Stroke respectively. The combined mortality rates are used to drive the progression of patient cohorts. Moreover, they are used to derive the revised annual death rates.

The revised annual death rates are finally calculated by age, sex and micro-vascular complication state module. The rates appropriate to individual morbid states are based on risk multipliers relative to non-diabetic mortality rates. The revised death rates are used as inputs in calculating transition rates in the neuropathy, nephropathy and retinopathy models.

#### **4.10.7 Progression of Patient Cohorts by Age and Survival**

The Framingham definitions of CVD, CHD and Stroke are used to estimate the progression of patient cohorts by age and survival.

The combined mortality rates and the proportions of new cases of CVD, CHD and Stroke are used to calculate the number of patients alive and dead by CVD, CHD and Stroke status, by age, sex and sub-cohort. Then, the total number of patients alive or dead is estimated as the sum of patients in all the sub-cohorts.

The average number of patients alive per 5-year age-group and by CVD, CHD and Stroke is derived from the previous estimates. This is then discounted at the cost rate.

Survival functions and lifetime healthcare costs are provided for each diagnosis sub-cohort. The survival functions are the percentage of patients alive by age and time from diagnosis (number of patients alive in each age group divided by the number of patients in outset). These functions are used to calculate the lifetime healthcare costs from diagnosis. The latter are later employed in the model to estimate the costs.

Finally, the number of: All, CHD and Stroke patients alive by time from diagnosis is calculated. This is twice the average number of patients alive in each sub-cohort for each 2.5/5 year time period following diagnosis for male and female patients. It is used later in the model to calculate the costs by time from diagnosis.

#### 4.10.8 Neuropathy sub-model

Eastman's neuropathy module is redesigned to incorporate peripheral vascular disease and neuropathy in accordance with the pathogenesis of foot ulceration and amputation defined by Boulton. The reformulation involved the identification of seven morbid states: no neuropathy, neuropathy, peripheral vascular disease, neuropathy and peripheral vascular disease, diabetic foot ulceration, first amputation and second amputation. The model employs linear functions with a WESDR threshold in the normal range of HbA1c to show the influence of glycaemic levels on transition rates (Alternatively, the user can use Eastman's power functions). The duration of diabetes is divided into two phases: initial and regular. The model produces a set of 5-year transition probabilities across all seven states of neuropathy by diagnosis group for each one of the phases.

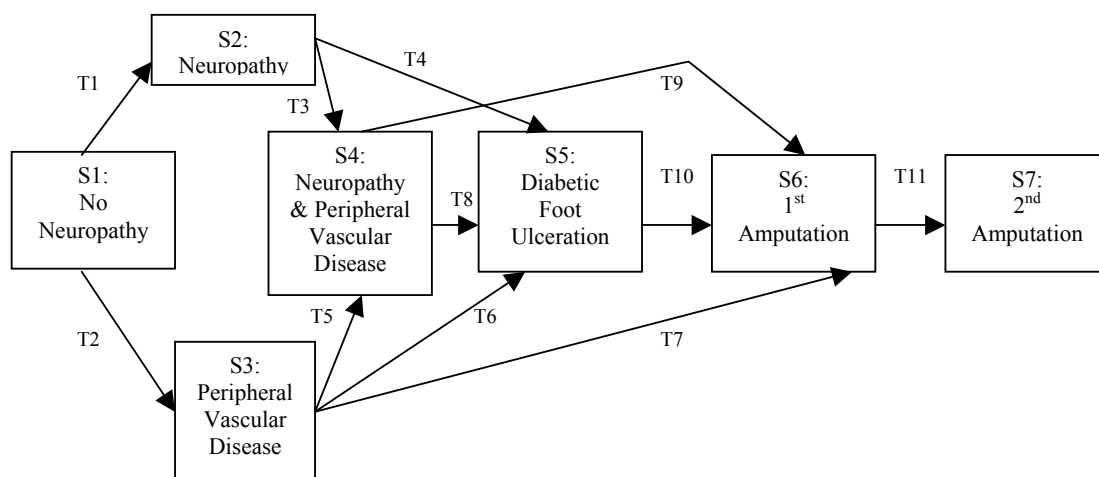
The neuropathy model assumes seven states of disease:

- No Disease
- Neuropathy
- Peripheral Vascular Disease (PVD)
- Neuropathy and Peripheral Vascular Disease
- Diabetic Foot Ulceration (DFU)
- 1<sup>st</sup> Amputation
- 2<sup>nd</sup> Amputation

These states are mutually exclusive and in any year, the patient can either remain in the same state, progress to another state or die.

The following diagram illustrates the neuropathy module:

Diagram 4: Neuropathy states



A person will first either develop neuropathy or peripheral vascular disease. This can then lead to diabetic foot ulceration and then 1st, 2nd and further amputations. Published annual rates of transition to neuropathic states are employed to derive 5-year state transition probabilities.

The elemental transition rates to Neuropathy state and to 2<sup>nd</sup> Amputation are identical to the ones used in Eastman's model.<sup>43,49</sup>

Two alternative sets of input transition rates can be used:

- Transition rates employed in Eastman's method
- Transition rates by fitting the same data to a linear function with thresholds.

The transition probabilities used in the model increase as the time since diagnosis of diabetes increases. The rates are calculated separately for each of the 30 age/sex diagnosis groups.

The transition probabilities are the net transition rates for a cohort of cases. While an individual patient might move from one state to any other within a year, at the level of net transitions a cohort can only progress to at most the next most severe state within one year. It is not possible to move from neuropathy only to peripheral vascular disease

The duration of diabetes is divided into two phases:

- *Initial phase*: This phase begins at diagnosis and ends at first 5-year age marker. Since diagnoses are made randomly in time, this phase lasts 2.5 years on average
- *Regular phase*: This phase follows the initial phase and lasts until death or age 100.

The model produces a set of 5-year transition probabilities across all seven states of neuropathy by diagnosis group. In addition, a modified set of transition rates is derived for the initial period from diagnosis of diabetes to the next model marker age.

Standard risks of developing significant neuropathy and peripheral vascular disease are provided. These are then adjusted by employing one of two alternative methods, so that the influence of glycaemic levels on transitions is demonstrated:

The Eastman power function method can be used. In this method, the rates are derived by Eastman by fitting the WESDR study results to an exponential curve and apply to the risk of developing neuropathy. The current HbA1c is standardised by dividing it by the standard HbA1c of 10.0 from DCCT data and raising it to a power parameter to fit the observations. Moreover, there is an option to adjust transition rates to neuropathy and PVD for ethnic mix variations.

Alternatively, the WESDR linear threshold can be used. In this method, the relationship between HbA1c and the annual risk of developing neuropathy is assumed to be linear, but with a threshold value (HbA1c of 6.0), below which the risk is zero. The basic annual transition rates are assumed to apply when HbA1c=10.0 and to increase linearly pro-rata to the excess of HbA1c above the threshold value (6.0).

In this model, the second method of the WESDR linear threshold is used for the central estimate.

Probabilities for eleven transitions are estimated using combination of the published and HbA1c adjusted rates included in the model. The methods applied to calculate the compound transition probabilities are correct.

Regular and initial probabilities are then calculated for each transition from one neuropathy state to the other. Residual proportions of patients in each disease state are estimated after transitions to more severe states and deaths.

A compound residue function is used to derive 5-year state transition probabilities for every possible pair of start and end states. These are derived by assigning a probability to each possible path from the start state to the end state and summing these probabilities across all pairs.

Finally, separate transition rates are derived for the initial phase between diagnosis and the first 5-year age marker using the early phase annual transition probabilities. Since a patient can be diagnosed with T2DM in any of the 5 preceding years, the initial phase lasts 2.5 years on average. For each combination of start state and end state the probability of this pair is calculated over 1,2,3,4, and 5 years. The average of these 5 probabilities is the “initial” transition matrix.

The 5-year neuropathy transition rates are used to calculate the numbers of patients in each state by age for each of the 30 age/sex diagnosis groups.

The newly diagnosed patients are distributed across the 7 neuropathic states. The model assumes the same distribution for all 30 diagnosis groups. In particular, of the newly diagnosed diabetics:

- 96.5% have no neuropathy and
- 3.5% has neuropathy.

The prevalence values used in the model are identical to the ones used by Eastman.<sup>43,49</sup>

The number of patients in each disease state at each age is determined by applying the 5-year state transition rates (analysed in the previous section) to the number of patients in the starting state in the previous period and adding up all the possible combinations. The initial rates are applied to the first transition (from outset to the first 5-year age mark). The regular rates apply thereafter until death or age 100. In addition, the number of patients in each state is adjusted so that the total number of patients alive (dead) matches the number predicted by the mortality / CVD module. This is done by adjusting pro-rata the number of patients in each state against the discrepancy in the overall number of patients alive.

The number of dead by state is calculated by applying the probability of death for that state to the number of patients in the state. These figures are again reconciled to match the values predicted in the mortality / CVD module.

The accumulated alive and dead by state at death derive directly from the two previous calculations. The total number of patients in each state at 5-year age points is estimated, by summing up all the initiation groups. The model provides the number of patients alive by neuropathy state and age-group for males, females and total. These figures are also discounted at the cost rate.

As far as the prevalence of neuropathy concerns, the model provides estimations for the following:

- Prevalence by age

- Prevalence by time from diagnosis
- Prevalent caseload by time from diagnosis
- Cumulative incidence by time from diagnosis

Finally, the model calculates the *number of patients in each state* ( $-N$ ,  $N$ ,  $PVD$ ,  $N\&PVD$ ,  $DFU$ ,  $1A$ ,  $2A$ ) by sub-cohort and time from diagnosis.

#### 4.10.9 Nephropathy

The nephropathy module follows Eastman’s formulation with four nephropathic states: no nephropathy, microalbuminuria, gross proteinuria and end-stage renal disease. The transition probabilities are adjusted to reproduce the main WESDR findings on cumulative incidence of the morbid states. The model employs linear functions with a WESDR threshold in the normal range of HbA1c to show the influence of glycaemic levels on transition rates (Alternatively, the user can use Eastman’s power functions). The duration of diabetes is divided into four phases: initial, early, middle and late. The model produces a set of 5-year transition probabilities across all four states of nephropathy by diagnosis group for each one of the phases.

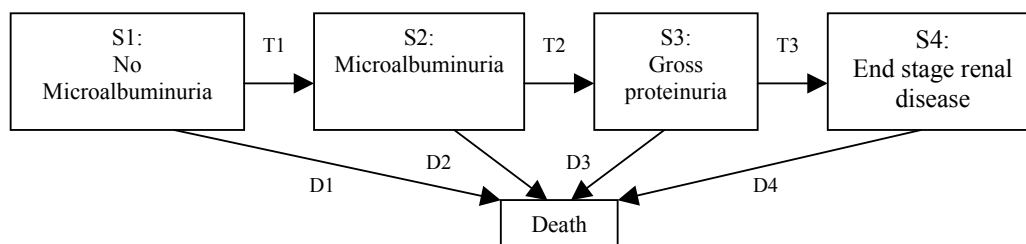
The nephropathy model assumes four states of disease:

- No disease
- Microalbuminuria (MA)
- Gross proteinuria (GPR)
- End-stage renal disease (ESRD)

These states are mutually exclusive and in any year, the patient can either remain in the same state, progress to the next more severe state or die.

The following diagram illustrates the nephropathy module:

Diagram 5: Nephropathy states



Published annual rates of transition to nephropathic states are employed to derive 5-year state transition probabilities. Two alternative sets of input transition rates can be used:

- Transition rates employed in Eastman’s method<sup>43,49</sup>
- Transition rates by fitting the same data to a linear function with thresholds.

The transition probabilities used in the model increase as the time since diagnosis of diabetes increases. The rates are calculated separately for each of the 30 age/sex diagnosis groups.

The transition probabilities are the net transition rates for a cohort of cases. While an individual patient might move from one state to any other within a year, at the level of net transitions a cohort can only progress to at most the next most severe state within one year. However, within 5-years, progression through all four stages is possible.

The duration of diabetes is divided into four phases:

- *Initial phase*: This phase begins at diagnosis and ends at first 5-year age marker. Since diagnoses are made randomly in time, this phase lasts 2.5 years on average
- *Early phase*: This phase follows the initial phase and lasts 10 years
- *Middle phase*: This phase follows the early phase and lasts 10 years
- *Late phase*: This phase follows the middle phase and lasts until death, or age 100.

The model produces a set of 5-year transition probabilities across all four states of nephropathy by diagnosis group for each of the early, middle and late periods since diagnosis. In addition, a modified set of early phase transition rates is derived for the initial period from diagnosis of diabetes to the next model marker age.

WESDR-based standard transition rates are provided in the model. These are the annual transition rates derived by adjusting the values reported by Eastman. The rates have been re-scaled to approximate outcomes reported by WESDR as part of the calibration of the model.

The transition rates used in GSK model are identical to the probabilities published in Eastman's model.

As mentioned earlier, the user can choose between two alternative sets of input transition rates, so that the influence of glycaemic levels on transitions is demonstrated:

The Eastman power function method can be used. In this method, the rates are derived by Eastman by fitting the WESDR study results to an exponential curve and apply to the risk of developing nephropathy. The current HbA1c is standardised by dividing it by the standard HbA1c of 10.0 from DCCT data and raising it to a power parameter to fit the observations. Moreover, there is an option to adjust transition rates to nephropathy and PVD for ethnic mix variations.

Alternatively, the WESDR linear threshold can be used. In this method, the relationship between HbA1c and the annual risk of developing nephropathy is assumed to be linear, but with a threshold value (HbA1c of 6.0), below which the risk is zero. The basic annual transition rates are assumed to apply when HbA1c=10.0 and to increase linearly pro-rata to the excess of HbA1c above the threshold value (6.0).

In this model, the second method of the WESDR linear threshold is used for the central estimate.

*Regular probabilities* are then calculated for each transition from one nephropathy state to the other for the initial, early, middle and late phase of the model. *Residual proportions* remaining in state after transitions and deaths occurring in one year are calculated in the model.

From the ESRD state there is no transition but to death. The nephropathy mortality rates are age and sex specific and are based on estimates of the relative risk of death for patients in the first three states as compared with non-diabetics. Though originally set to figures used by Eastman, these have been modified as part of the model calibration process to match published outcomes. The mortality rates for patients in the ESRD are extracted from Eastman's paper<sup>43,49</sup> and were derived from a dialysis register in the US. The proportions are calculated by sex and each progression phase.

A compound residue function is used to derive *5-year state transition probabilities* for every possible pair of start and end states. These are derived by assigning a probability to each possible path from the start state to the end state and summing these probabilities across all pairs. Each year is an independent event therefore the probability of a particular 5-year path is the product of annual probabilities of remaining in the same state, progression to the next state or dying. This process is repeated for the early, middle and late phases and the rates are referred to as the "*regular*" transition rates.

As mentioned earlier, separate transition rates are derived for the initial phase between diagnosis and the first 5-year age marker, using the early phase annual transition probabilities. Since a patient can be diagnosed with T2DM in any of the 5 preceding years, the initial phase lasts 2.5 years on average. For each combination of start state and end state the probability of this pair is calculated over 1,2,3,4, and 5 years. The average of these 5 probabilities is the "*initial*" transition matrix.

The method employed in the model to estimate the transition probabilities is correct.

The 5-year nephropathy transition rates are used to calculate the number of patients in each state by age for each of the 30 age/sex diagnosis groups.

The newly diagnosed patients are distributed across the 4 nephropathic states. The model assumes the same distribution for all 30 diagnosis groups. In particular, of the newly diagnosed diabetics:

- 87.1% have no nephropathy,
- 11% have microalbuminuria and
- 1.9% has gross proteinuria.

The prevalence of microalbuminuria used in the model is identical to the one used by Eastman.<sup>43,49</sup>

The number of patients in each disease state at each age is determined by applying the 5-year state transition rates (analysed in the previous section) to the number of patients in the starting state in the previous period and adding up all the possible combinations. The initial rates are applied to the first transition (from outset to the first 5-year age mark). The early rates are applied to the next two transitions (next 10 years), the middle rates to the following two transitions (next 10 years) and the late rates apply thereafter until death or age 100. In addition, the number of patients in each state is adjusted so that the total number of patients alive (dead) matches the number predicted by the mortality / CVD module. This is done by adjusting pro-rata

the number of patients in each state against the discrepancy in the overall number of patients alive.

The number of dead by state is calculated by applying the probability of death for that state to the number of patients in the state. These figures are again reconciled to match the values predicted in the mortality / CVD module.

The accumulated alive and dead by state at death are derived directly from the two previous calculations.

The total number of patients in each state at 5-year age points is then derived, by summing up all the initiation groups.

Moreover, the number of new cases per annum of GPR by transition phase and gender is estimated from prevalent cases and transition rates. The model provides the number of patients alive by nephropathy state and age-group for males, females and total. These figures are also discounted at the cost and then at the outcome rate.

As far as the prevalence of nephropathy concerns, the model provides estimations for the following:

- Prevalence by age
- Prevalence by time from diagnosis
- Prevalent caseload by time from diagnosis
- Cumulative incidence by time from diagnosis

Finally, the model calculates the number of patients in each state (-MA, +MA, GPR, ESRD) by sub-cohort and time from diagnosis.

#### **4.10.10 Retinopathy**

Eastman's retinopathy module is redesigned to represent combinations of possible conditions and severities. Eighteen compound transition rates were calculated from five elemental transition probabilities. The structure comprises nine distinct morbid states: no retinopathy, background diabetic retinopathy, macular oedema (MO), MO with blindness in one eye, proliferative diabetic retinopathy (PDR), PDR with blindness in one eye, MO and PDR, MO and PDR with blindness in one eye and blindness in both eyes. The model employs linear functions with a WESDR threshold in the normal range of HbA1c to show the influence of glycaemic levels on transition rates (Alternatively, the user can use Eastman's power functions). The duration of diabetes is divided into four phases: early, middle, late and continuing. The model produces a set of 5-year transition probabilities across all nine states of retinopathy by diagnosis group for each one of the phases.

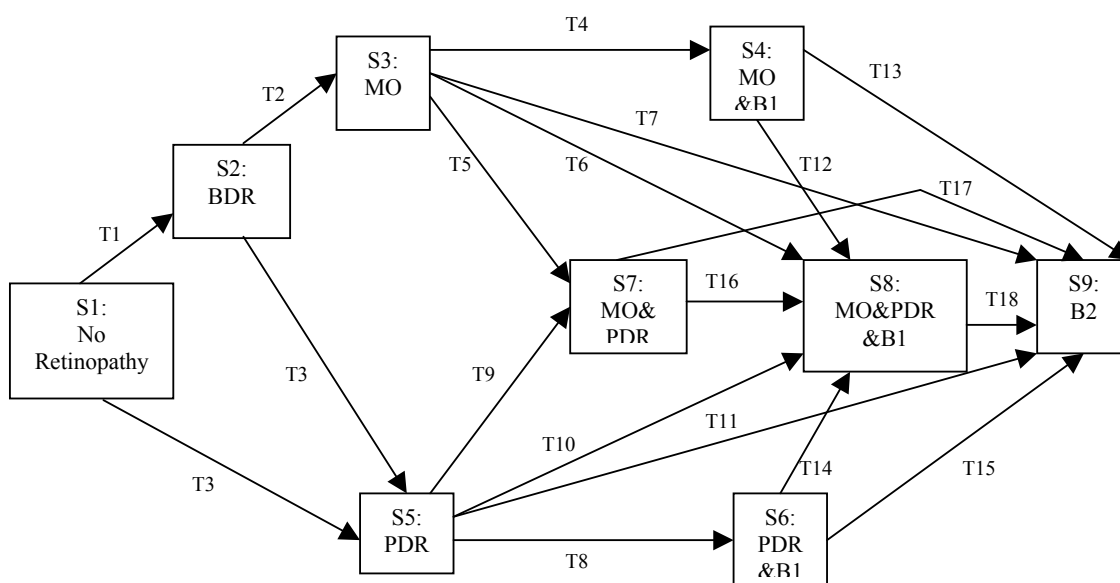
The retinopathy model assumes nine states of disease:

- No disease,
- Background diabetic retinopathy (BDR),
- Macular oedema (MO),

- Macular oedema with blindness in one eye (MO&B1),
- Proliferative diabetic retinopathy (PDR),
- Proliferative diabetic retinopathy with blindness in one eye (PDR&B1),
- Macular oedema and proliferative diabetic retinopathy (MO&PDR),
- Macular oedema and proliferative diabetic retinopathy with blindness in one eye (MO&PDR&B1) and
- Blindness in both eyes (B2).

These states are mutually exclusive and in any year, the patient can either remain in the same state, progress to another state or die. The following diagram illustrates the retinopathy module:

Diagram 6: Retinopathy states



Published annual rates of transition to retinopathic states are employed to derive 5-year state transition probabilities.

Two alternative sets of input transition rates can be used:

- Transition rates employed in Eastman’s method
- Transition rates by fitting the same data to a linear function with thresholds.

The transition probabilities used in the model increase as the time since diagnosis of diabetes increases. The rates are calculated separately for each of the 30 age/sex diagnosis groups.

The transition probabilities are the net transition rates for a cohort of cases. While an individual patient might move from one state to any other within a year, at the level of net transitions a cohort can only progress to at most the next most severe state within one year.

The duration of diabetes is divided into four phases:

- Early phase: This phase begins at diagnosis and ends at the first 5-year age marker. Since diagnoses are made randomly in time, this phase lasts 2.5 years on average
- Middle phase: This phase follows the early phase and lasts for 10 years.
- Late phase: This phase follows the middle phase and lasts for 10 years.
- Continuing phase: This phase follows the late phase and lasts until death or age 100.

It is assumed that transition rates for retinopathy and macular oedema are statistically independent.

The model produces a set of 5-year transition probabilities across all nine states of retinopathy by diagnosis group. In addition, a modified set of transition rates is derived for the initial period from diagnosis of diabetes to the next model marker age. In this module, the early phase coincides with the initial period, so no 5-year transition rates are calculated for the early phase.

A total of 18 distinct transition probabilities are used, derived from 5 underlying probabilities.

Annual risks of developing MO and PDR blindness are provided with and without photocoagulation treatment. Moreover, the standard risks of developing BDR, MO and PDR are calculated for the early, middle, late and final stages. The original Eastman hazard rates were amended to calibrate outcomes against WESDR results.

The risks of developing BDR, ME, PDR and blindness that are used to calculate the transition probabilities are provided in the model. The elemental hazard rates used for the estimation of the transitions to non-proliferative retinopathy, proliferative retinopathy, macular oedema and blindness are identical to the ones used by Eastman.<sup>43,49</sup>

Multipliers then calibrate these rates, in order to achieve an approximation to published WESDR incidence and prevalence rates.

The values of these basic parameters depend on the choice of glycaemia gradient (Eastman or WESDR) and are adjusted for current mean HbA1c values and ethnic mix variations. In particular:

The Eastman power function method can be used. In this method, the rates are derived by Eastman by fitting the WESDR study results to an exponential curve and apply to the risk of developing neuropathy. The current HbA1c is standardised by dividing it by the standard HbA1c of 10.0 from DCCT data and raising it to a power parameter to fit the observations. Moreover, there is an option to adjust transition rates to neuropathy and PVD for ethnic mix variations.

Alternatively, the WESDR linear threshold can be used. In this method, the relationship between HbA1c and the annual risk of developing neuropathy is assumed to be linear, but with a threshold value (HbA1c of 5.35 for “normal to BDR” and 7.0 for “BDR to MO” & “BDR to PDR”), below which the risk is zero. The basic annual transition rates are assumed to apply when HbA1c=10.0 and to increase linearly pro-rata to the excess of HbA1c above the threshold value (6.0).

In this model, the second method of the WESDR linear threshold is used for the central estimate.

Transition probabilities are then calculated for the early, middle, late and final phases of the model, using the basic model parameters mentioned above, the WESDR linear threshold method and assuming independent probabilities.

The methods applied to calculate the compound transition probabilities are correct.

Residual proportions of patients in each disease state are estimated after transitions to more severe states and deaths. A compound residue function is used to derive 5-year state transition probabilities for every possible pair of start and end states. These are derived by assigning a probability to each possible path from the start state to the end state and summing these probabilities across all pairs. The transition probabilities are estimated for each one of the middle, late and final phases of the disease.

Finally, separate transition rates are derived for the initial phase between diagnosis and the first 5-year age marker using the early phase annual transition probabilities. Since a patient can be diagnosed with T2DM in any of the 5 preceding years, the initial phase lasts 2.5 years on average. For each combination of start state and end state the probability of this pair is calculated over 1,2,3,4, and 5 years. The average of these 5 probabilities is the “initial” transition matrix.

The 5-year neuropathy transition rates are used to calculate the numbers of patients in each state by age for each of the 30 age/sex diagnosis groups.

The newly diagnosed patients are distributed across the 9 retinopathic states. The model assumes the same distribution for all 30 diagnosis groups. In particular, of the newly diagnosed diabetics:

- 80.0% has no background diabetic retinopathy and
- 20.0% has background diabetic retinopathy.

The prevalence values used in the model are identical to the one used by Eastman.<sup>43,49</sup>

The number of patients in each disease state at each age is determined by applying the 5-year state transition rates (analysed in the previous section) to the number of patients in the starting state in the previous period and adding up all the possible combinations. The initial rates are applied to the first transition (from outset to the first 5-year age mark). The regular rates apply thereafter until death or age 100. In addition, the number of patients in each state is adjusted, so that the total number of patients alive (dead) matches the number predicted by the mortality / CVD module. This is done by adjusting pro-rata the number of patients in each state against the discrepancy in the overall number of patients alive.

The number of dead by state is calculated by applying the probability of death for that state to the number of patients in the state. These figures are again reconciled to match the values predicted in the mortality / CVD module.

The accumulated alive and dead by state at death derive directly from the two previous calculations.

The total number of patients in each state at 5-year age points is estimated, by summing up all the initiation groups.

The model provides the number of patients alive by retinopathy state and age-group for males, females and total. These figures are also discounted at the cost rate.

As far as the prevalence of retinopathy concerns, the model provides estimations for the states: background retinopathy, MO, MO and PDR, blind in one eye and blind in both eyes. In particular, the following are calculated:

- Prevalent caseload: estimated number of patients in some states by age band and transition phase
- Prevalence by age (in 5-year age points)
- Prevalence by time from diagnosis
- Prevalent caseload by time from diagnosis
- Cumulative incidence by time from diagnosis

Finally, the model calculates the number of patients in each state (-R, BDR, MO, PDR, MO&B1, PDR&B1, MO&PDR, MO/PDR&B1, B2) by sub-cohort and time from diagnosis.

#### **4.10.11 Hypoglycaemia**

The model estimates the number of hypoglycaemic events per annum in the cohort by age and sex. However, these estimates are not linked to the costing module, as the latter includes the cost of hypoglycaemia implicitly within the excess cost of diabetes.

It is assumed that DCCT relationships between mean HbA1c and incidence of hypoglycaemia apply (as used by Eastman).

The number of severe hypoglycaemic events (requiring medical attention) expected per year by age group and sex is calculated by multiplying period event rates by the average number of patients. The period event rates are weighted average event rates applicable to the 2.5/5-year periods used in the model and are based on the annual event rates. The latter are calculated as the average of the treatment-specific event rates, weighted by the proportions of patients receiving each mode of treatment. The treatment specific event rates are calculated using DCCT relationships as employed by Eastman.

#### **4.10.12 Weight gain**

The weight gain is included in the model indirectly. In particular, body mass index is one of the variables that are used to calculate blood pressure. The latter is then employed in the model in order to estimate the cardio-vascular disease death rates. It was not feasible to interfere in the model and single out the effect of change in the body mass index only.

#### **4.10.13 Cataract and Cancer**

The model estimates the prevalence of cancer and cataract in the diabetic cohort, based on analysis of the South Glamorgan data. Cataract prevalence is estimated by fitting a simple linear regression model to the actual rates of cataract. Cancer prevalence is calculated by fitting an exponential model for males and a simple linear regression model for females to the actual rates of cancer.

The model provides estimates of Cataract and Cancer in the diabetic cohort by age and sex. Relationships are based on analysis of South Glamorgan data, which are assumed to be representative.

The number of cataract operations per year by age and sex is calculated among patients with Type II diabetes. In particular, the number of patients alive in each age group is multiplied by the excess of the average HbA1c above a threshold of 5% and an assumed gradient of 0.2% per 1% increase in HbA1c. These estimates are descriptive only and are not linked to other parts of the model.

Simple linear regression models were fitted to the actual rates of cataract prevalence from the South Glamorgan data, in order to obtain model equations and estimate prevalence by age and sex.

The coefficient of determination (R-squared) in the above two models was considerably high (75% and 95% respectively), indicating that the models have sufficiently fitted the South Glamorgan data.

An exponential model for males and a simple linear regression model for females were fitted to the actual rates of cancer prevalence from the South Glamorgan data, in order to obtain model equations and estimate prevalence by age.

The coefficient of determination (R-squared) in the above two models was considerably high (86% and 73% respectively), indicating that the models have sufficiently fitted the South Glamorgan data.

#### **4.10.14 Multi-Morbidity**

The model estimates the number of patients suffering from more than one of the five major complication states of diabetes (CHD, stroke, blindness in one or both eyes, chronic DFU and/or LEA and ESRD). Frequencies of multiple complications are derived from analysis of the Cardiff database of South Glamorgan residents. These frequencies and univariate prevalence values of the above complication states are used to calculate the prevalence of every possible combination of the conditions.

The model estimates the proportions of male and female patients with Type II diabetes who suffer from various combinations of the five most severe complication states:

- Coronary heart disease
- Stroke
- Blindness in one or both eyes

- Chronic diabetic foot ulceration and/or lower extremity amputation
- End stage renal disease

The frequencies of multiple complications are assumed to be those derived from analysis of the Cardiff database of South Glamorgan residents.

The univariate prevalence by age of the above complication states is used to calculate the crude prevalence of every combination of the conditions. Each possible combination is represented by a set of 0's/1's. These are combined with the five separate univariate prevalences, to yield the probability of patients having the specified combination of complications, assuming statistical independence. Finally, the resulting figure is multiplied by the relative probability factor derived from analysis of the Cardiff database, to represent the relative frequencies of different combinations. This prevalence is then adjusted, by dividing the prevalence of every combination of the condition by the total per age group, in order to standardise the sum of probabilities in each age-range to unity.

The probabilities for the number of morbidities present by age and sex is then calculated, by adding together the appropriate adjusted prevalences for the 0,1,2,3,4 and 5 serious morbid conditions.

Finally, the total number of patients with 0,1,2,3,4 and 5 morbidities present is estimated by multiplying the number of patients alive at each age group by the probabilities for the number of morbidities present.

The method employed to calculate the prevalence and number of morbidities is appropriate.

#### **4.10.15 Cost Aspects**

Costs are in 2000 UK Pounds.

The main costing areas included within the models are as follows:

- Inpatient costs;
- Outpatient costs;
- Primary care costs;
- Drug costs.

##### *Inpatient Costs*

Hospital admissions are assigned by primary diagnosis to one of nine broad categories (diabetes, nephropathy, retinopathy, neuropathy and skin infections, heart disease, stroke, cancer, cataract and other diseases). A polynomial or exponential model is employed to calculate the annual admission rate and average length of stay by age. Hospital costs are calculated from a fixed cost per admission plus a variable cost per bed-day. The cost parameters are derived from National NHS speciality costs for the dominant specialities for each costing category.

Age/sex models for admission rates and length of stay are derived from original analysis of Cardiff database of South Glamorgan residents.

In-patient costs consist of a fixed treatment cost per admission plus a variable cost dependent on the length of hospital stay. Generally, day case admissions are assumed to incur the fixed cost and a nominal half-day length of stay. Admission rates vary by age, sex and diabetic status, whereas the unit costs are common to all categories of patients.

The number of male and female admissions per annum / 1,000 is calculated by age and for each disease state, using polynomial and exponential model coefficients for 4 years. Thus, the total number of admissions can be then calculated as the sum of the individual admissions.

The male and female average length of stay is calculated by age and for each disease state, using polynomial model coefficients. Thus, the total bed days and the overall length of stay are then estimated. The former is the length of stay multiplied by the number of admissions in each case and the latter is the total bed days over the total admissions in each case.

In-patient cost parameters are provided by disease state for an admission (fixed treatment cost) and for a bed day (variable cost). These are presented in the following table:

**Table 33: In-patient costs by morbid state per admission and length of stay**

Disease/complication	per Admission	per Bed-day
Diabetes	£420	£136
Nephropathy	£696	£129
Retinopathy	£680	£180
Neuropathy/skin infection	£180	£204
Heart disease	£904	£156
Stroke	£518	£147
Cancer	£267	£204
Cataract	£260	£200
Other diseases	£300	£140

In-patient unit costs derived from CIPFA English Trust Financial Returns 1995/1996.

Total In-Patient costs over all years of life are calculated by age, sex, disease state and diabetic status. The cost data in the table above, the number of patients alive and the number of patients in individual disease states are used for the calculations. Moreover, the number of admissions to micro-vascular states is estimated by multiples of non-diabetic rates, which reflect the overall diabetic admission rates. *Annual In-Patient cost per patient alive* is also provided by age, sex and diabetic status. The mentioned costs are then discounted at cost rate.

Finally, the discounted In-Patient costs by time from diagnosis are estimated by sex, diabetic status and time from diagnosis.

### *Out-patient Treatment Costs*

Attendances and outpatient costs are estimated for patients identified as suffering from one of eight disease conditions (CHD, stroke, neuropathy, nephropathy, retinopathy, cataract, cancer and other diseases). A polynomial or exponential model is employed to calculate the number of attendances for each of nine U.K. outpatient specialties. The cost parameters are derived from National NHS speciality-specific clinic costs.

The UK Out-Patient specialties are represented in the following 9 broad groups, which are assumed to be homogenous:

- General Medicine, Geriatrics, Haematology
- Ophthalmology
- Obs & Gynaecology
- Cardiology, Cardiothoracic surgery
- General Surgery, Trauma & Orthopaedic, Dermatology, Rehab
- Radiotherapy, Anaesthetics
- Mental Handicap & Mental Illness
- Neurology, Neurosurgery
- Ear, Nose & Throat, Urology, Rheumatology

The model Out-Patient activity is calculated through the following 8 disease drivers:

- CHD
- Stroke
- Neuropathy
- Nephropathy
- Retinopathy
- Cataract
- Cancer
- Other

Overall Cardiff Out-Patient data were decomposed into incremental additive models to resource use within each specialty group, with a residue associated only with patient numbers. Since driver models are incremental, they are not constrained to non-negative values. Therefore, results should only be interpreted in aggregate form.

Age/sex models for attendance rates are derived from original analysis of Cardiff database of South Glamorgan residents.

Polynomial and other model coefficients of attendances for 4 years are used to estimate the number of male and female attendances per annum/1,000 by age, specialty group and by condition.

Out-Patient unit costs derived from CIPFA English Trust Financial Returns 1995/96.

Costs per Out-patient attendance and per specialty are provided in the model. These costs are used to calculate the average outpatient costs for males and females. Relative activity weights are assigned to individual specialties within each group based on activity volumes in the Cardiff database. The average costs per specialty are presented in the following table:

**Table 34: Out-patient costs per specialty**

Specialty Grouping	Male Diabetics	Female Diabetics
GM/Ger/Haem/Thor	£84.59	£85.42
Ophthalmology	£49.00	£49.00
Obs & Gynaecology	-	£72.13
Cardiology/Ctsurgery	£75.35	£75.32
Derm/GS/Rehab/T&O	£66.44	£65.95
Anaes/RT/Pall	£90.52	£92.65
MH/MI	£104.87	£106.31
Neurology/Neurosurg	£117.78	£117.40
ENT/Rheum/Urology	£68.05	£68.61

The model provides estimations for the total cost of outpatient care by age-group, sex, diabetic status and major complication/disease. These are based on attendance rates, unit costs and patient numbers. Attendance rate weights for micro-vascular are used to exclude “no complication” states from the calculation of attendance numbers. Moreover, the excess cost due to diabetes is calculated, as well as the overall attendance rates for diabetic and non-diabetic patients for 1,000 per year. These costs are then discounted at the cost rate.

Finally, the model estimates the undiscounted costs of outpatient care by sex, diabetic status, major complication/disease and time from diagnosis.

#### *Primary Care Services Costs*

The proportion of GP consultations attributable to type 2 diabetes is assumed to be the same as the proportion of prescriptions dispensed to type 2 diabetic patients. The number of GP consultations is estimated using age-related curves (exponential model) from the General Practice Morbidity Database Project (GPMDP). The average cost per GP consultation is assumed to be £12 (Personal Social Services Research Unit, PSSRU).

The proportion of GP consultations attributable to type 2 diabetes is assumed to be the same as the proportion of prescriptions dispensed to type 2 diabetic patients.

The average cost per GP consultation is assumed to be £12.

Coefficients from polynomial models are used to calculate the number of GP consultations per annum per person by age, sex and diabetic status. The latter are then employed to estimate the total over all years of life GP consultations by age, sex and diabetic status. Finally, multiplying

the total consultations by the average cost of a GP consultation derives the total cost of GP consultations by age and sex. This is then discounted at the cost rate.

Moreover, the total cost of GP consultation by sex and time from diagnosis is calculated, by multiplying the consultation rates by the number of patients alive by time from diagnosis. This is then discounted at the cost rate.

Unit costs are derived from PSSRU “Health and Social Services Costs”.

### *Community Health Costs*

The proportion of community health contacts attributable to type 2 diabetes is assumed to be the same as the proportion of prescriptions dispensed to type 2 diabetic patients. The number of community health contacts is estimated using age-related curves (exponential model) from GPMDP. The contacts are calculated per health professional (chiropodist, dietician, practice nurse and other) and costed with data from PSSRU.

The proportion of Community Health contacts attributable to type 2 diabetes is assumed to be the same as the proportion of prescriptions dispensed to type 2 diabetic patients.

Coefficients from polynomial models and the proportion of diabetic prescriptions for type 2 diabetes are used to calculate the community health contacts per annum per person by age, sex and diabetic status. In particular, number of contacts is calculated for chiropodists, dieticians, practice nurse and others.

Unit costs are derived from PSSRU “Health and Social Services Costs”.

The average contacts per referral and the average cost per contact employed in the model are presented in the following table:

**Table 35: Average community health contacts and costs**

Professional	Average Contacts Per Referral	Average Cost per Contact
Chiropodist	6	£11.5
Dietician	3	£9.0
Practice nurse	2	£6.0
Other	4	£10.0

The Community Health contacts per annum by age, sex, diabetic status and type of contact are calculated by multiplying the number of contacts by the number of patients alive. These are then multiplied by the respective costs to give the Community Health costs per annum by age, sex, diabetic status and by type of contact. The contacts and the costs are also discounted at the cost rate.

The Community Health costs per annum by sex, diabetic and time from diagnosis are also provided. They are calculated by multiplying the number of contacts by the number of patients alive and contact rates and costs.

### *Drug Costs*

A logistic model from Tayside prescriptions paper is used to calculate the proportion of diabetic prescriptions attributable to type 2 diabetes. These are then employed in polynomial age-related models, in order to estimate the number of prescriptions. The average cost of prescriptions (excl. drugs for diabetes) is derived from the Tayside paper and is assumed to be £8.90 for diabetics.

Average prescriptions per annum by age and sex are calculated, using polynomial model coefficients multiplied by the proportion of diabetic prescriptions attributable to type 2 diabetes. The proportion of diabetic prescriptions is calculated using logistic model coefficients. The model is based on data from Tayside prescriptions paper. Total prescriptions per annum by age and sex are then provided, by multiplying the average prescriptions by the number of patients alive. These are then discounted at cost rate.

The average cost of prescriptions (excluding drugs for diabetes) is £8.8961 for diabetics and £8.7311 for non-diabetics. The source used is the Tayside diabetes paper (type 2 only).

The total cost of prescriptions is then calculated multiplying the total prescriptions by their average cost. The cost is also adjusted for inflation changes. The total cost of prescriptions is also discounted at cost rate.

The total cost of prescriptions by time from diagnosis is calculated by multiplying the prescribing rates by the number of patients alive by time from diagnosis and the average costs.

The cost of diabetic therapy by age, sex and type of therapy is estimated by multiplying the average annual medication cost by the number of patients treated with this medication. This cost is then discounted. Moreover, the same cost is provided by time from diagnosis.

### *Costs*

The in-patient, outpatient, primary and drug costs estimated in the previous sections are summarised and the following costs are additionally calculated:

- Total costs by age and sex (undiscounted and discounted)
- Total costs by time of diagnosis and by sex (undiscounted and discounted)
- 1-year total costs per patient alive
- Lifetime healthcare costs from diagnosis by age and sex
- Aggregate total costs for each type of cost by sex (undiscounted and discounted)
- Total cost per survival year
- Total cost per person

#### 4.10.16 Clinical outcomes

The model provides the following outputs:

- Average age at diagnosis and death by sex
- Average survival by sex
- Average life expectancy by age at diagnosis and sex
- Patients alive by time from diagnosis and sex (number and proportion)
- Years of life (discounted at outcomes rate and undiscounted) by sex in the following states:
  - Nephropathic
  - Neuropathic
  - Retinopathic
  - CHD
  - Stroke
- Proportion of patients in state of each complication by sex

The GSK model estimates mean life expectancy, total lifetime costs, costs per LYG and incremental cost per QALY.

#### 4.10.17 Utility Scores

##### *QALYs VAS*

Utility values recently available from the CODE-2 study are employed and a multivariate model of EuroQol Visual Analogue Scores is generated. The latter is used to calculate the mean QALY scores in the model.

A multivariate model of EuroQol Visual Analogue Scores derived from CODE-2 data together with cohort details are used to calculate the mean QALY score for patients in each diagnosis sub-cohort by age and sex and for each model time-period. Moreover, mean scores applying across each 2.5/5-year model period from diagnosis for each sub-cohort by age are estimated by averaging figures from VAS scores calculated earlier.

The CODE-2 EuroQol responses are representative of a general population of persons with type II diabetes and offer the patient perspective.

The model used to calculate the QALY scores consists of an exponential equation. The percentage of patients in each morbid state is multiplied by the model coefficients and they are all summed together with the constant of the model. The model is additionally adjusted for age characteristics. The exponential of this sum is then calculated (plus some adjustments) to provide the QALY score of the model.

The coefficients used in the model are presented in the following table:

**Table 36: EuroQol VAS model coefficients**

<b>EuroQol VAS</b>	<b>Model Coefficients</b>
Constant	4.40500
ESRD	-0.45700
Insulin	-0.19700
Stroke	-0.19200
Amputation/FU	-0.13100
Retinopathy	-0.12060
PVD only	-0.10100
Proteinuria	-0.09630
Female	-0.09080
Tablets	-0.06060
CHD	-0.03250
Age	-0.00221

*QALYs EQ*

Utility values recently available from the CODE-2 study are employed and a multivariate model of EuroQol E2-5D Scores is generated. The latter is used to calculate the mean QALY scores in the model.

A multivariate model of EuroQol E2-5D Scores derived from CODE-2 data together with cohort details are used to calculate the mean QALY score for patients in each diagnosis sub-cohort by age and sex and for each model time-period. Moreover, mean scores applying across each 2.5/5-year model period from diagnosis for each sub-cohort by age are estimated by averaging figures from VAS scores calculated earlier.

The CODE-2 EuroQol responses are representative of a general population of persons with type 2 diabetes and offer the societal perspective.

The model used to calculate the QALY scores consists of an exponential equation. The percentage of patients in each morbid state is multiplied by the model coefficients and they are all summed together with the constant of the model. The model is additionally adjusted for age characteristics. The exponential of this sum is then calculated (plus some adjustments) to provide the QALY score of the model.

The coefficients used in the model are presented in the following table:

**Table 37: EuroQol EQ5-D model coefficients**

<b>EuroQol EQ5-D</b>	<b>Model Coefficients</b>
Constant	-0.002133
Nephropathy	-0.130000
Insulin	-0.074230
Stroke	-0.165000
Amputation	-0.207000
Foot ulcer	-0.182000
Retinopathy	-0.027160
Blind	-0.153000
PVD only	-0.088640
Tablets	-0.021130
CHD	-0.013150
Age	-0.001758

The following QALY calculations were performed in the model:

- QALYs from time of diagnosis to death (discounted at outcomes rate and undiscounted) by sex: Two different utility measures were used, derived from the following sources:
  - o CODE-2
  - o EuroQol data
- Life-years by time from diagnosis and sex: These are split down for each complication state.
- QALYs – VAS by time from diagnosis: These are aggregated QALYs using the Visual Analogue Scale (discounted at outcomes rate and undiscounted) for by sex and time from diagnosis.
- QALYs – EQ by time from diagnosis: These are aggregated QALYs using the EQ-5D scale (discounted at outcomes rate and undiscounted) for by sex and time from diagnosis.

#### **4.11 VALIDATION OF THE GSK MODEL**

##### **4.11.1 Assumptions made within the GSK model**

In the absence of available type 2 data, type 1 diabetes data have been used in its place.

Again, the submission states that a weakness exists in that, for the AMI sub-model, calculations were based on a predominantly white population, and, therefore, the population used may not be representative of the diabetic population.

##### **4.11.2 Conclusions on the critical appraisal of the GSK model<sup>28</sup>**

The model proposed by GSK contains a detailed representation of diabetic health states. The model presented by GSK is almost identical in structure to the model proposed by Bagust.<sup>47</sup> The only significant difference is in the HbA1c module. As explained earlier, GSK metabolic model estimates the glucose levels for each period after diagnosis, based on an impaired insulin

sensitivity and a declining beta-cell function. The levels of those two variables depend on the effect of the treatment applied. Patients move to the next therapy in the treatment pathway, when their glucose level increases to a certain level. On the other hand, the Bagust HbA1c module is a distinct Markovian sub-model, which incorporates annual transition rates to indicate the change from one treatment to another.

There are two main criticisms of the GSK submission.

- There was no transparency in the presentation of the model. A lot of data was included in the model, for which no information or explanation was provided in the form of a report.
- The company performed no sensitivity analysis. Given the complexity of the model and the large number of parameters, this is a critical failing in establishing the credibility of the favourable economic outcomes. Specifically, the stability of the results and identification of key drivers would be of greatest value.

#### 4.12 KEY ECONOMIC RESULTS FOR ROSIGLITAZONE

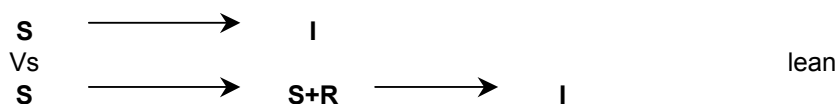
The economic model described by GSK is used to investigate the use of rosiglitazone as an adjunctive therapy when monotherapy has failed to achieve an adequate level of control of average blood glucose levels. The two indications as detailed in the licensing documentation are examined:

- where metformin is contra-indicated and where the use of sulphonylurea has failed to achieve adequate control (defined in the model analysis as HbA1c > 7.5%) the choices evaluated are to add rosiglitazone to sulphonylurea or to switch to insulin therapy.
- in obese patients who have failed to achieve adequate glycaemic control with metformin the alternatives evaluated are to add rosiglitazone or sulphonylurea to metformin.

GSK has compared several scenarios of treatment pathways and the cost-effectiveness results are presented below:

Note: all the costs and QALYs included in the tables are cumulative per 1,000 patients.

- Lean patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:

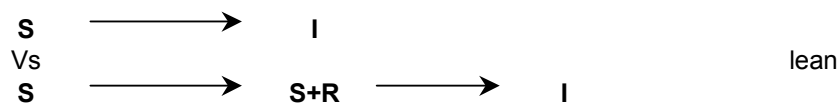


**Table 38 : Cost per QALY of adding Rosi to SU (lean)**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-470,619	204.6	N/A	-229,686	171.3	N/A
22.5	12.5	-465,676	207.3	N/A	-228,116	173.3	N/A
27.5	17.5	-465,278	207.5	N/A	-228,022	173.5	N/A
32.5	22.5	-466,076	207.4	N/A	-228,163	173.4	N/A
	20	-465,677	207.5	N/A	-228,093	173.5	N/A

This comparison reveals that rosiglitazone dominates in both cost and efficacy outcomes, as the cost of the scenario that adds rosiglitazone is lower than the cost of the scenario that progresses directly to insulin after sulphonylurea. Thus, in lean patients on a sulphonylurea who are contra-indicated to or intolerant to metformin, then adding rosiglitazone after mono-therapy failure is a cost effective strategy.

We have used the model to calculate the above figures and we found exactly the same results. In addition, we have generated the respective incremental cost-effectiveness ratios, by using Life Years Gained (LYG) instead of Quality Adjusted Life Years (QALYs). The results are presented below:



**Table 39: Cost per LYG of adding Rosi to SU (lean)**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	LYG	ICER	Costs 6%	LYGs 1.5%	ICER
17.5	7.5	-470,619	1.7	N/A	-229,686	1.4	N/A
22.5	12.5	-465,676	3.8	N/A	-228,116	2.9	N/A
27.5	17.5	-465,278	4.1	N/A	-228,022	3.1	N/A
32.5	22.5	-466,076	3.8	N/A	-228,163	2.9	N/A
	20	-465,677	3.9	N/A	-228,093	3.0	N/A

We observe that the conclusion remains the same: adding rosiglitazone after mono-therapy failure with sulphonylurea is preferable than progressing directly to insulin. Although the gain in life years is insignificant, the cost of rosiglitazone combination therapy is lower than the cost of insulin and this makes the second scenario dominant.

Finally, we have verified that the mechanism to calculate the QALYs and the LYG in the model works properly. In particular, we have set all the utility values equal to zero and found exactly the same life years results as the ones presented in the model.

- Obese patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:



**Table 40: Cost per QALY of adding Rosi to SU (obese)**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-439,172	204.3	N/A	-196,501	171.1	N/A
22.5	12.5	-433,541	207.3	N/A	-194,713	173.3	N/A
27.5	17.5	-431,161	208.2	N/A	-194,148	173.9	N/A
32.5	22.5	-429,914	208.6	N/A	-193,927	174.2	N/A
	20	-430,538	208.4	N/A	-194,038	174.1	N/A

This comparison reveals that rosiglitazone dominates in both cost and efficacy outcomes, as the cost of the scenario that adds rosiglitazone is lower than the cost of the scenario that progresses directly to insulin after sulphonylurea. Thus, in obese patients on a sulphonylurea who are contra-indicated to or intolerant to metformin, then adding rosiglitazone after mono-therapy failure is a cost effective strategy.

We have used the model to calculate the above figures and we found exactly the same results.

In addition, we have generated the respective incremental cost-effectiveness ratios, by using Life Years Gained (LYG) instead of Quality Adjusted Life Years (QALYs). The results are presented below:



**Table 41: Cost per LYG of adding Rosi to SU (obese)**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	LYG	ICER	Costs 6%	LYGs 1.5%	ICER
17.5	7.5	-439,172	1.7	N/A	-196,501	1.4	N/A
22.5	12.5	-433,541	4.2	N/A	-194,713	3.2	N/A
27.5	17.5	-431,161	5.4	N/A	-194,148	4.0	N/A
32.5	22.5	-429,914	6.0	N/A	-193,927	4.4	N/A
	20	-430,538	5.7	N/A	-194,038	4.2	N/A

We observe that the conclusion remains the same: adding rosiglitazone after mono-therapy failure with sulphonylurea is preferable than progressing directly to insulin. Although the gain in life years is insignificant, the cost of rosiglitazone combination therapy is lower than the cost of insulin and this makes the second scenario dominant.

Finally, we have verified that the mechanism to calculate the QALYs and the LYG in the model works properly. In particular, we have set all the utility values equal to zero and found exactly the same life years results as the ones presented in the model.

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin.



**Table 42: Cost per QALY of adding Rosi to Met**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-658,971	292.0	N/A	-317,472	241.5	N/A
22.5	12.5	-573,369	377.1	N/A	-290,294	305.0	N/A
27.5	17.5	-519,917	398.1	N/A	-277,613	319.5	N/A
32.5	22.5	-488,060	406.1	N/A	-271,967	324.6	N/A
	20	-503,988	402.1	N/A	-274,790	322.1	N/A

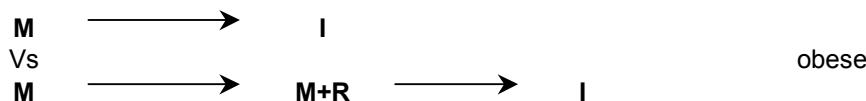
To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

This comparison reveals that rosiglitazone dominates in both cost and efficacy outcomes, as the cost of the scenario that adds rosiglitazone is lower than the cost of the scenario that progresses directly to insulin after metformin. Thus, in obese patients on metformin whose physicians do

not want to prescribe sulphonylureas, then adding rosiglitazone after mono-therapy failure is a cost effective strategy.

We have used the model to calculate the above figures and we found exactly the same results.

In addition, we have generated the respective incremental cost-effectiveness ratios, by using Life Years Gained (LYG) instead of Quality Adjusted Life Years (QALYs). The results are presented below:



**Table 43: Cost per LYG of adding Rosi to Met**

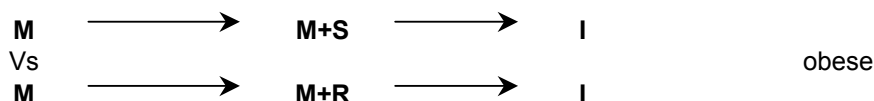
Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	LYG	ICER	Costs 6%	LYG 1.5%	ICER
17.5	7.5	-658,971	3.4	N/A	-317,472	2.8	N/A
22.5	12.5	-573,369	19.0	N/A	-290,294	14.3	N/A
27.5	17.5	-519,917	40.8	N/A	-277,613	29.4	N/A
32.5	22.5	-488,060	54.4	N/A	-271,967	38.2	N/A
	20	-503,988	47.6	N/A	-274,790	33.8	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

We observe that the conclusion remains the same: adding rosiglitazone after mono-therapy failure with metformin is preferable than progressing directly to insulin. Although the gain in life years is insignificant, the cost of rosiglitazone combination therapy is lower than the cost of insulin and this makes the second scenario dominant.

Finally, we have verified that the mechanism to calculate the QALYs and the LYG in the model works properly. In particular, we have set all the utility values equal to zero and found exactly the same life years results as the ones presented in the model.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin.



**Table 44: Cost per QALY of Met + SU versus Met + Rosi**

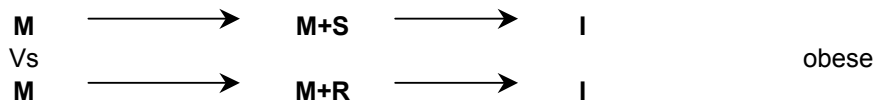
Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,449,421	89.1	16,274	713,459	71.5	9,972
22.5	12.5	1,532,021	170.8	8,968	739,684	132.5	5,582
27.5	17.5	1,575,845	188.5	8,361	750,081	144.7	5,183
32.5	22.5	1,597,716	193.7	8,248	753,956	148.1	5,091
	20	1,586,781	191.1	8,303	752,019	146.4	5,137

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

This comparison reveals that rosiglitazone improves efficacy levels when added to metformin after mono-therapy failure, compared to adding sulphonylureas. Thus, in obese patients on metformin who are able to take sulphonylureas, adding rosiglitazone after mono-therapy failure is a cost effective option, with an incremental ratio of £5,137/QALY at 20 years.

We have used the model to calculate the above figures and we found exactly the same results.

In addition, we have generated the respective incremental cost-effectiveness ratios, by using Life Years Gained (LYG) instead of Quality Adjusted Life Years (QALYs). The results are presented below:



**Table 45: Cost per LYG of Met + SU versus Met + Rosi**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	LYG	ICER	Costs 6%	LYG 1.5%	ICER
17.5	7.5	1,449,421	3.4	430,095	713,459	2.7	262,253
22.5	12.5	1,532,021	16.9	90,773	739,684	12.8	57,851
27.5	17.5	1,575,845	34.1	46,175	750,081	24.7	30,352
32.5	22.5	1,597,716	43.3	36,894	753,956	30.6	24,627
	20	1,586,781	38.7	40,984	752,019	27.7	27,184

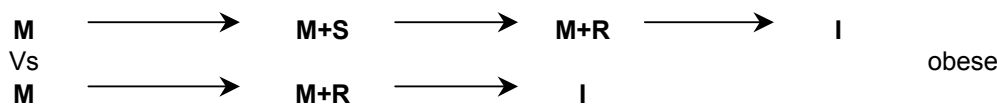
To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The above table demonstrate that the scenario including rosiglitazone is not cost-effective. Adding rosiglitazone after mono-therapy failure with metformin is not a cost effective option,

compared to adding sulphonylurea. The cost of rosiglitazone combination therapy is very big compared to the cost of sulphonylurea combination therapy. Moreover, the gain in life years of using rosiglitazone therapy is insignificant. Thus, we observe very high incremental cost-effectiveness ratios, which reach the £430,095.

Finally, we have verified that the mechanism to calculate the QALYs and the LYG in the model works properly. In particular, we have set all the utility values equal to zero and found exactly the same life years results as the ones presented in the model.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then switching to rosiglitazone:



**Table 46: Cost per QALY of switching from Met + SU to Met + Rosi**

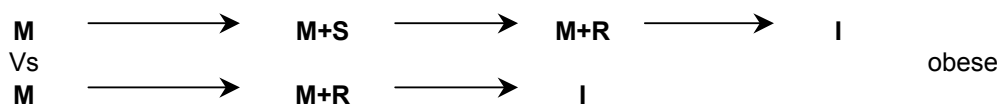
Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,482,499	76.4	19,417	727,504	61.4	11,857
22.5	12.5	1,506,582	138.0	10,917	735,150	107.3	6,850
27.5	17.5	1,538,948	146.9	10,480	742,830	113.4	6,549
32.5	22.5	1,556,219	151.4	10,276	745,889	116.4	6,411
	20	1,547,584	149.1	10,376	744,359	114.9	6,479

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

This comparison reveals that rosiglitazone improves efficacy levels when added to metformin after mono-therapy failure, compared to adding rosiglitazone after combination therapy of metformin plus sulphonylurea. Thus, in obese patients on metformin who are able to take sulphonylureas, adding rosiglitazone after mono-therapy failure is a cost effective option compared to introducing sulphonylurea and then switching to rosiglitazone. The incremental cost-effectiveness ratio for this comparison is £6,479/QALY at 20 years.

We have used the model to calculate the cost-effectiveness for each of these scenarios and we obtained the same results.

In addition, we have generated the respective incremental cost-effectiveness ratios, by using Life Years Gained (LYG) instead of Quality Adjusted Life Years (QALYs). The results are presented below:



**Table 47: Cost per LYG of switching from Met + SU to Met + Rosi**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	LYG	ICER	Costs 6%	LYG 1.5%	ICER
17.5	7.5	1,482,499	3.5	428,221	727,504	2.8	259,591
22.5	12.5	1,506,582	14.5	104,013	735,150	11.0	66,771
27.5	17.5	1,538,948	27.0	56,994	742,830	19.7	37,770
32.5	22.5	1,556,219	34.5	45,067	745,889	24.5	30,437
	20	1,547,584	30.8	50,301	744,359	22.1	33,702

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The above table indicates that the scenario including rosiglitazone is not cost-effective. Adding rosiglitazone after mono-therapy failure with metformin is not a cost effective option, compared to adding sulphonylurea and then switching to rosiglitazone. The cost of rosiglitazone combination therapy is very big compared to the cost of sulphonylurea combination therapy. Moreover, the gain in life years of using rosiglitazone therapy is insignificant. Thus, we observe very high incremental cost-effectiveness ratios, which reach £259,591.

Finally, we have verified that the mechanism to calculate the QALYs and the LYG in the model works properly. In particular, we have set all the utility values equal to zero and found exactly the same life years results as the ones presented in the model.

#### 4.12.1 Sensitivity Analysis on the HbA1c Threshold

We have performed a sensitivity analysis on the HbA1c threshold of switching therapies. In particular, we have changed the threshold from HbA1c=7.5% to HbA1c=8.5%. The results of our analysis concerning the cost effectiveness of rosiglitazone are presented below:

- Lean patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:

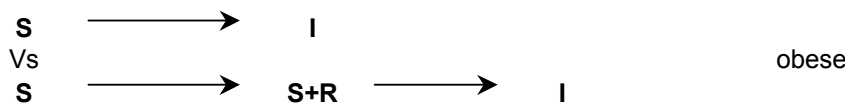


**Table 48: Cost per QALY of adding Rosi to SU (lean) using 8.5% threshold**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
27.5	7.5	-28,328	722.6	N/A	-104,938	70.9	N/A
32.5	12.5	-263,244	425.5	N/A	-103,497	72.5	N/A
37.5	17.5	-333,143	233.0	N/A	-103,054	72.9	N/A
42.5	22.5	-340,507	136.2	N/A	-102,941	73.1	N/A
	20	-336,825	184.6	N/A	-102,998	73.0	N/A

We observe that the conclusion remains the same: rosiglitazone dominates in both cost and quality adjusted life years in this scenario.

- Obese patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:

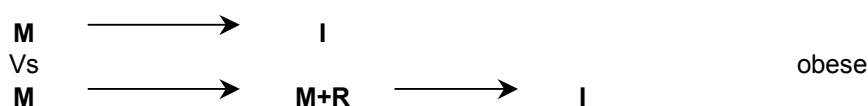


**Table 49: Cost per QALY of adding Rosi to SU (obese) using 8.5% threshold**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
27.5	7.5	-282,840	95.5	N/A	-82,116	5,845.4	N/A
32.5	12.5	-282,715	96.3	N/A	-82,094	5,070.1	N/A
37.5	17.5	-281,342	96.6	N/A	-81,912	4,286.1	N/A
42.5	22.5	-280,508	96.8	N/A	-90,829	3,614.1	N/A
	20	-280,925	96.7	N/A	-86,371	3,950.1	N/A

Adding rosiglitazone after sulphonylurea mono-therapy failure dominates the scenario of progressing immediately to insulin. The change in threshold has not affected the final conclusion.

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin:



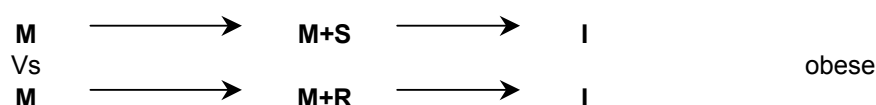
**Table 50: Cost per QALY of adding Rosi to Met using 8.5% threshold**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
27.5	7.5	-228,952	143.1	N/A	-60,024	102.5	N/A
32.5	12.5	-275,321	180.8	N/A	-68,244	126.7	N/A
37.5	17.5	-225,257	192.8	N/A	-61,612	133.8	N/A
42.5	22.5	-206,675	196.3	N/A	-59,774	146.3	N/A
	20	-215,966	194.6	N/A	-60,693	140.0	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

Adding rosiglitazone after metformin mono-therapy failure dominates the scenario of progressing immediately to insulin. The change in threshold has not affected the final conclusion.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin:



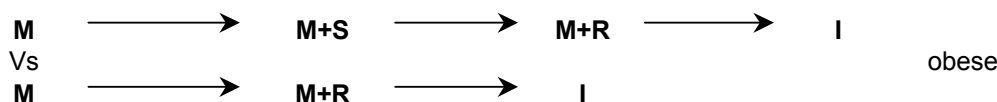
**Table 51: Cost per QALY of Met + SU versus Met + Rosi using 8.5% threshold**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
27.5	7.5	498,865	46.9	10,636	129,107	32.8	3,937
32.5	12.5	449,172	83.1	5,407	120,297	56.0	2,147
37.5	17.5	496,202	94.4	5,258	126,527	62.8	2,016
42.5	22.5	513,143	97.6	5,258	128,205	75.1	1,708
	20	504,672	96.0	5,258	127,366	68.9	1,848

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

Adding rosiglitazone instead of sulphonylurea after metformin mono-therapy failure remains a cost-effective strategy even with a change in the switching threshold (Table 51 versus Table 44). Moreover, the cost-effectiveness is now improved, as the incremental ratios are lower than the ones observed before the change in threshold.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then switching to rosiglitazone:



**Table 52: Cost per QALY of switching from Met + SU to Met + Rosi using 8.5% threshold**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
27.5	7.5	539,161	7.8	69,092	139,213	5.6	24,962
32.5	12.5	539,200	14.5	37,189	139,220	15.9	8,766
37.5	17.5	550,187	17.1	32,083	140,676	11.5	12,282
42.5	22.5	554,951	18.0	30,808	141,146	22.4	6,291
	20	552,569	17.6	31,430	140,911	16.9	8,316

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

This comparison indicates that the incremental cost-effectiveness ratios have significantly increased after the increase in the glycaemia threshold (Table 52 versus Table 46). However, adding rosiglitazone to metformin after mono-therapy failure is still cost-effective compared to adding first sulphonylurea and then switch to insulin after the change in threshold; the discounted cost-effectiveness ratio is less than £30,000 (£24,962).

### Sensitivity Analysis on the Treatment Effects

We have performed sensitivity analysis on the treatment effects, in order to investigate the impact that variations in the calibrators have in the cost-effectiveness results presented in GSK submission. We concentrated on the scenarios that include rosiglitazone combination therapy.

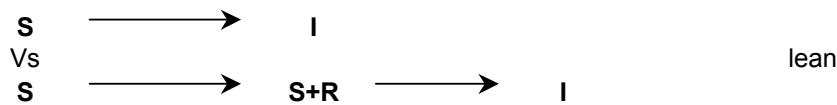
All the changes we made refer to the treatment effect of rosiglitazone. In particular, we have varied the effects of rosiglitazone treatment on Insulin Sensitivity and Beta Cell Function.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

We have examined exactly the same scenarios that were presented in the previous sections:

- Lean patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:

- Change of Insulin Sensitivity:



*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:

**Table 53: Cost per QALY of adding Rosi to SU (lean) following change in IS**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-320,347	199.5	N/A	-165,612	167.2	N/A
22.5	12.5	-335,575	196.4	N/A	-170,447	164.9	N/A
27.5	17.5	-344,893	193.7	N/A	-172,657	163.0	N/A
32.5	22.5	-351,078	192.0	N/A	-173,754	162.0	N/A
	20	-347,986	192.9	N/A	-173,206	162.5	N/A

We observe that the difference in costs between the two scenarios has decreased compared to the results before the change in the effect (Table 53 versus Table 38). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Change of Beta Cell Function:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 54: Cost per QALY of adding Rosi to SU (lean) following change in Beta cell**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-317,731	200.5	N/A	-164,526	168.0	N/A
22.5	12.5	-328,518	198.5	N/A	-167,951	166.5	N/A
27.5	17.5	-336,325	196.1	N/A	-169,803	164.9	N/A
32.5	22.5	-342,059	194.5	N/A	-170,820	163.9	N/A
	20	-339,192	195.3	N/A	-170,312	164.4	N/A

We observe that the difference in costs between the two scenarios has decreased compared to the results before the change in the effect (Table 54 versus Table 38). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:
  - Change of Insulin Sensitivity:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 55: Cost per QALY of adding Rosi to SU (obese) following change in IS**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-337,220	202.0	N/A	-153,133	169.3	N/A
22.5	12.5	-341,065	202.1	N/A	-154,353	169.3	N/A
27.5	17.5	-343,938	201.2	N/A	-155,035	168.7	N/A
32.5	22.5	-346,117	200.6	N/A	-155,422	168.3	N/A
	20	-345,028	200.9	N/A	-155,229	168.5	N/A

We observe that the difference in costs between the two scenarios has decreased compared to the results before the change in the effect (Table 55 versus Table 40). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Change of Beta Cell Function:

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The results are presented below:

**Table 56: Cost per QALY of adding Rosi to SU (obese) following change in Beta cell**



Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-336,266	202.4	N/A	-152,733	169.6	N/A
22.5	12.5	-338,532	202.9	N/A	-153,452	170.0	N/A
27.5	17.5	-340,905	202.2	N/A	-154,015	169.5	N/A
32.5	22.5	-342,938	201.7	N/A	-154,376	169.1	N/A
	20	-341,922	202.0	N/A	-154,196	169.3	N/A

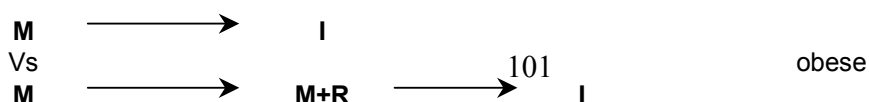
We observe that the difference in costs between the two scenarios has decreased compared to the results before the change in the effect (Table 56 versus Table 40). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin:

- Change of Insulin Sensitivity:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 57: Cost per QALY of adding Rosi to Met following change in IS**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-305,465	195.1	N/A	-166,509	163.6	N/A
22.5	12.5	-327,856	190.3	N/A	-173,618	160.0	N/A
27.5	17.5	-335,726	187.9	N/A	-175,486	158.3	N/A
32.5	22.5	-338,351	187.1	N/A	-175,951	157.8	N/A
	20	-337,039	187.5	N/A	-175,718	158.1	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The results indicate that the difference in costs between the two scenarios has considerably decreased compared to the results before the sensitivity analysis (Table 57 versus Table 42). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with metformin and the number of QALYs is greater.

▪ Change of Beta Cell Function:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 58: Cost per QALY of adding Rosi to Met following change in Beta cell**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-357,983	196.7	N/A	-188,923	164.9	N/A
22.5	12.5	-374,933	193.4	N/A	-194,304	162.4	N/A
27.5	17.5	-380,128	191.8	N/A	-195,537	161.3	N/A
32.5	22.5	-381,276	191.4	N/A	-195,740	161.0	N/A
	20	-380,702	191.6	N/A	-195,638	161.2	N/A

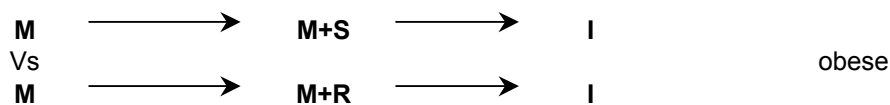
To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The results indicate that the difference in costs between the two scenarios has considerably decreased compared to the results before the sensitivity analysis (Table 58 versus Table 42). However, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with metformin and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin:
  - Change of Insulin Sensitivity:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 59: Cost per QALY of Met + SU versus Met + Rosi following change in IS**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,802,927	-7.8	N/A	864,422	-6.4	N/A
22.5	12.5	1,777,534	-16.0	N/A	856,360	-12.5	N/A
27.5	17.5	1,760,036	-21.7	N/A	852,208	-16.4	N/A
32.5	22.5	1,747,425	-25.3	N/A	849,973	-18.8	N/A
	20	1,753,730	-23.5	N/A	851,090	-17.6	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

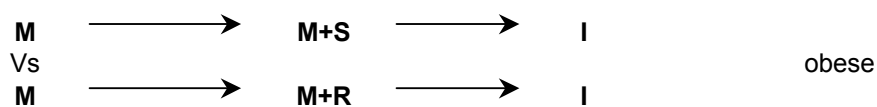
We observe that the scenario of adding rosiglitazone instead of sulphonylureas after monotherapy failure with metformin is no longer cost-effective after the change in the treatment effect (Table 59 versus Table 44). In particular, it is dominated by the scenario of adding sulphonylureas, as the QALYs of this scenario are greater than the one with rosiglitazone.

Hence, we conclude that the investigation of this comparison of scenarios proves to be significantly sensitive to changes on the treatment effects.

- Change of Beta Cell Function:

The results are presented below:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*



**Table 60: Cost per QALY of Met + SU versus Met + Rosi following change in Beta cell**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,750,410	-6.2	N/A	842,008	-5.1	N/A
22.5	12.5	1,730,457	-12.9	N/A	835,674	-10.1	N/A
27.5	17.5	1,715,635	-17.8	N/A	832,157	-13.4	N/A
32.5	22.5	1,704,500	-21.0	N/A	830,183	-15.5	N/A
	20	1,710,067	-19.4	N/A	831,170	-14.5	N/A

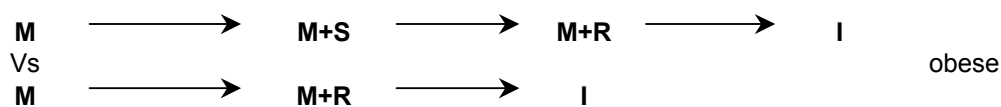
To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

We observe that the scenario of adding rosiglitazone instead of sulphonylureas after monotherapy failure with metformin is no longer cost-effective after the change in the treatment effect (Table 60 versus Table 44). In particular, it is dominated by the scenario of adding sulphonylurea, as the QALYs of this scenario are greater than the one with rosiglitazone.

Hence, we conclude that the investigation of this comparison of scenarios proves to be significantly sensitive to changes on the treatment effects.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then switching to rosiglitazone:
  - Change of Insulin Sensitivity:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.* The results are presented below:



**Table 61: Cost per QALY of switching from Met + SU to Met + Rosi following change in IS**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,842,385	-7.1	N/A	881,133	-11.8	N/A
22.5	12.5	1,819,052	-13.8	N/A	873,726	-10.8	N/A
27.5	17.5	1,809,773	-16.7	N/A	871,524	-12.8	N/A
32.5	22.5	1,807,713	-17.5	N/A	871,159	-13.3	N/A
	20	1,808,743	-17.1	N/A	871,342	-13.1	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

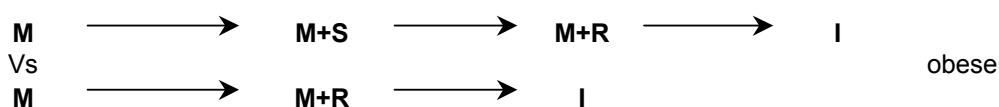
The results indicate that the scenario of adding rosiglitazone directly after monotherapy failure with metformin is no longer cost-effective after the sensitivity analysis performed (Table 61 versus Table 46). In particular, it is dominated by the scenario of adding first sulphonylurea and then switching to rosiglitazone after failure of combination therapy with sulphonylurea, as the QALYs of this scenario are greater than the one with direct adding of rosiglitazone.

Hence, we conclude that the investigation of this comparison of scenarios proves to be significantly sensitive to changes on the treatment effects.

- Change of Beta Cell Function:

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results are presented below:



**Table 62 Cost per QALY of switching from Met + SU to Met + Rosi following change in Beta cell**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,789,855	-5.5	N/A	858,714	-4.5	N/A
22.5	12.5	1,768,742	-11.6	N/A	852,011	-9.1	N/A
27.5	17.5	1,757,395	-14.6	N/A	849,319	-11.2	N/A
32.5	22.5	1,755,386	-15.3	N/A	848,963	-11.6	N/A
	20	1,756,390	-15.0	N/A	849,141	-11.4	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The results indicate that the scenario of adding rosiglitazone directly after monotherapy failure with metformin is no more cost-effective after the sensitivity analysis performed (Table 62 versus Table 46) . In particular, it is dominated by the scenario of adding first sulphonylurea and then switching to rosiglitazone after failure of combination therapy with sulphonylurea, as the QALYs of this scenario are greater than the one with direct adding of rosiglitazone.

Hence, we conclude that the investigation of this comparison of scenarios proves to be significantly sensitive to changes on the treatment effects.

#### 4.12.2 Sensitivity Analysis on the Inpatient Costs

We have performed sensitivity analysis on the in-patient costs, as these consist the biggest part of the total health costs. In particular, we have assumed the following in-patient costs by disease state:

**Table 63: Sensitivity analysis on the inpatient costs**

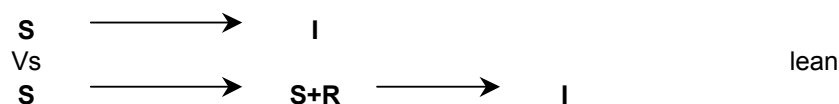
Disease/complication	Inpatient Cost Per Year
Diabetes	£218
Nephropathy	£1,478
Retinopathy	£480
Neuropathy/skin infection	£1,264
Heart disease	£1,320
Stroke	£1,791
Cataract	£1,073

Source: HRG reference costs 2001

We have left the cost parameters for cancer and other diseases unchanged.

We have examined exactly the same scenarios that were presented in the previous sections:

- Lean patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:



**Table 64: Cost per QALY of adding Rosi to SU (lean) following change in inpatient costs**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-470,852	204.6	N/A	-229,778	171.3	N/A
22.5	12.5	-466,446	207.3	N/A	-228,380	173.3	N/A
27.5	17.5	-466,105	207.5	N/A	-228,299	173.5	N/A
32.5	22.5	-466,829	207.4	N/A	-228,427	173.4	N/A
	20	-466,467	207.5	N/A	-228,363	173.5	N/A

We observe that the difference in costs is almost identical as before the sensitivity analysis was performed (Table 64 versus Table 38). Although the absolute costs of the two scenarios have now decreased, their difference remains almost the same. Thus, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:



**Table 65: Cost per QALY of adding Rosi to SU (obese) following change in inpatient costs**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-439,434	204.3	N/A	-196,611	171.1	N/A
22.5	12.5	-434,385	207.3	N/A	-195,007	173.3	N/A
27.5	17.5	-432,240	208.2	N/A	-194,499	173.9	N/A
32.5	22.5	-431,108	208.6	N/A	-194,298	174.2	N/A
	20	-431,674	208.4	N/A	-194,399	174.1	N/A

We observe that the difference in costs is almost identical as before the sensitivity analysis was performed (Table 65 versus Table 40). Although the absolute costs of the two scenarios have now decreased, their difference remains almost the same. Thus, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with sulphonylurea and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin:



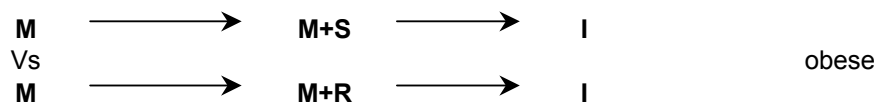
**Table 66: Cost per QALY of adding Rosi to Met following change in inpatient costs**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	-659,332	292.0	N/A	-317,622	241.5	N/A
22.5	12.5	-576,334	377.1	N/A	-291,271	305.0	N/A
27.5	17.5	-527,573	398.1	N/A	-279,703	319.5	N/A
32.5	22.5	-498,882	406.1	N/A	-274,617	324.6	N/A
	20	-513,228	402.1	N/A	-277,160	322.1	N/A

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

We observe that the difference in costs is almost identical as before the sensitivity analysis was performed (Table 66 versus Table 42). Although the absolute costs of the two scenarios have now decreased, their difference remains almost the same. Thus, the scenario of adding rosiglitazone still dominates in both cost and efficacy outcomes, as its cost is lower than the cost of progressing immediately to insulin after failure in monotherapy with metformin and the number of QALYs is greater.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin:



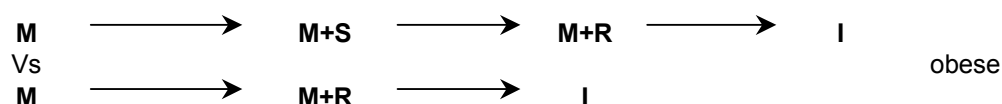
**Table 67: Cost per QALY of Met + Su versus Met + Rosi following change in inpatient costs**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,449,038	89.1	16,270	713,304	71.6	9,968
22.5	12.5	1,529,229	170.8	8,951	738,764	132.5	5,575
27.5	17.5	1,569,218	188.5	8,326	748,252	144.7	5,170
32.5	22.5	1,588,863	193.7	8,202	751,734	148.1	5,076
	20	1,579,041	191.1	8,263	749,993	146.4	5,123

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

We observe that the difference in costs is almost identical as before the sensitivity analysis was performed (Table 67 versus Table 44). Although the absolute costs of the two scenarios have now decreased, their difference remains almost the same. The scenario of adding rosiglitazone instead of sulphonylureas after monotherapy failure with metformin remains cost-effective after the change in the in-patient costs.

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then switching to rosiglitazone:



**Table 68: Cost per QALY of switching from Met + SU to Met + Rosi following change in inpatient costs**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,482,083	76.4	19,411	727,334	61.4	11,854
22.5	12.5	1,504,106	138.0	10,899	734,326	107.3	6,842
27.5	17.5	1,533,688	146.9	10,444	741,345	113.4	6,535
32.5	22.5	1,549,267	151.4	10,234	744,107	116.4	6,395
	20	1,541,478	149.1	10,337	742,726	114.9	6,464

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

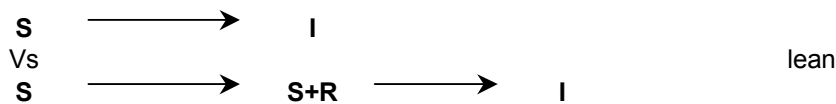
We observe that the difference in costs is almost identical as before the sensitivity analysis was performed (Table 68 versus Table 46). Although the absolute costs of the two scenarios have now decreased, their difference remains almost the same. Thus, the scenario of adding rosiglitazone directly after monotherapy failure with metformin remains cost-effective after the sensitivity analysis performed compared to the scenario of adding first sulphonylurea and then switching to rosiglitazone after failure of combination therapy with sulphonylurea.

#### 4.12.3 Sensitivity Analysis on the Insulin Cost

We have performed sensitivity analysis on the annual cost of insulin treatment. In particular, we have reduced insulin cost by 50%, in order to investigate possible changes in the cost-effectiveness results. Thus, we have set the insulin cost equal to £305.59.

We have examined exactly the same scenarios that were presented in the previous sections:

- Lean patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:



**Table 69: Cost per QALY of adding Rosi to SU (lean) after changing insulin cost**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	351,591	204.6	1,718	171,159	171.3	999
22.5	12.5	355,837	207.3	1,717	172,508	173.3	995
27.5	17.5	356,149	207.5	1,716	172,581	173.5	995
32.5	22.5	355,449	207.4	1,714	172,458	173.4	994
	20	355,799	207.5	1,715	172,520	173.5	995

The table above demonstrates that after the change in the cost of insulin treatment the rosiglitazone scenario is not dominant any more (Table 69 versus Table 38). The results indicate that the addition of rosiglitazone after monotherapy failure with sulphonylurea has higher cost than progressing immediately to insulin after monotherapy failure. However, it is a cost-effective option, as the incremental cost-effectiveness ratios are very low (average of 996).

- Obese patients uncontrolled on maximum dose of sulphonylurea, unable to take metformin. Comparing addition of rosiglitazone to progression to insulin:

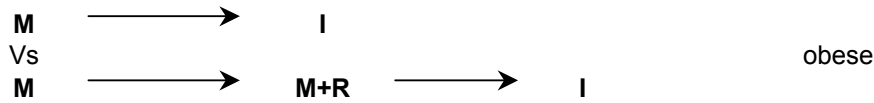


**Table 70: Cost per QALY of adding Rosi to SU (obese) after changing insulin cost**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	328,942	204.3	1,610	147,003	171.1	859
22.5	12.5	333,742	207.3	1,610	148,527	173.3	857
27.5	17.5	335,728	208.2	1,613	148,999	173.9	857
32.5	22.5	336,770	208.6	1,614	149,183	174.2	856
	20	336,249	208.4	1,613	149,091	174.1	856

The table above demonstrates that after the change in the cost of insulin treatment the rosiglitazone scenario is not dominant any more (Table 70 versus Table 40). The results indicate that the addition of rosiglitazone after monotherapy failure with sulphonylurea has higher cost than progressing immediately to insulin after monotherapy failure. However, it is a cost-effective option, as the incremental cost-effectiveness ratios are very low (average of 857).

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin:



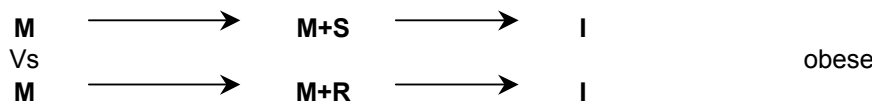
**Table 71: Cost per QALY of adding Rosi to Met after changing insulin cost**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	861,734	292.0	2,951	414,269	241.5	1,715
22.5	12.5	1,043,727	377.1	2,767	472,050	305.0	1,548
27.5	17.5	1,096,565	398.1	2,755	484,586	319.5	1,517
32.5	22.5	1,123,832	406.1	2,767	489,419	324.6	1,508
	20	1,110,198	402.1	2,761	487,002	322.1	1,512

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.

The sensitivity analysis demonstrated that rosiglitazone combination therapy with metformin does not dominate the alternative scenario of progressing directly to insulin after metformin failure (Table 71 versus Table 42). The table results indicate that the addition of rosiglitazone after monotherapy failure with metformin has higher cost than progressing immediately to insulin after monotherapy failure. However, it is a cost-effective option, as the incremental cost-effectiveness ratios are very low (average of 1,560).

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin:



**Table 72: Cost per QALY of Met + SU versus Met + Rosi after changing insulin cost**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	1,634,376	89.1	18,351	792,041	71.5	11,070
22.5	12.5	1,814,055	170.8	10,619	849,087	132.5	6,407
27.5	17.5	1,858,804	188.5	9,862	859,705	144.7	5,940
32.5	22.5	1,877,575	193.7	9,692	863,032	148.1	5,828
	20	1,868,189	191.1	9,776	861,368	146.4	5,884

To achieve a realistic output representative of the U.K for rosiglitazone license and use, GSK has apportioned the final costs and effects at 85% for 4mg and 15% for 8mg.



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Thus, in this section, we compare the several scenarios, by assuming that 100% of rosiglitazone is seen in the 8mg dose.

The scenarios we compare are the ones that include metformin:

- Obese patients uncontrolled on maximum dose of metformin and not prescribed sulphonylurea. Comparing addition of rosiglitazone to progression to insulin:

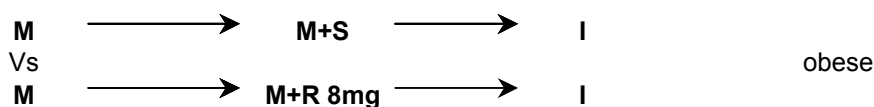


**Table 74: Cost per QALY of adding Rosi to Met (obese) using 8mg dose**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	818,962	304.6	2,689	392,194	251.8	1,558
22.5	12.5	1,255,955	461.5	2,722	530,934	368.7	1,440
27.5	17.5	1,411,696	542.3	2,603	567,883	424.7	1,337
32.5	22.5	1,514,910	567.8	2,668	586,164	441.0	1,329
	20	1,463,303	555.0	2,636	577,024	432.9	1,333

The sensitivity analysis demonstrated that the scenario of adding rosiglitazone of 8mg after failure of mono-therapy with metformin does not dominate the scenario of progressing directly to insulin therapy (Table 74 versus Table 42). The results indicate that the cost of the second scenario is now higher than the cost of the first scenario. However, the strategy of adding rosiglitazone after metformin failure is a cost-effective option compared to progressing to insulin, as the incremental cost-effectiveness ratios are very low in all cases (average of 1,399).

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then progressing to insulin:

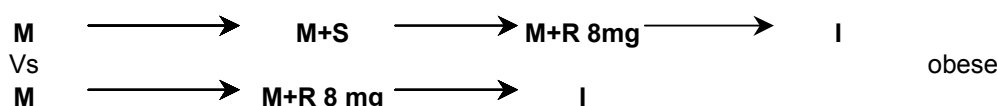


**Table 75: Cost per QALY of Met + SU versus Met + Rosi using 8mg dose**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	2,927,354	101.7	28,798	1,423,125	81.8	17,389
22.5	12.5	3,361,345	255.2	13,174	1,560,912	196.3	7,953
27.5	17.5	3,507,458	332.7	10,543	1,595,577	249.9	6,384
32.5	22.5	3,600,686	355.4	10,132	1,612,087	264.5	6,095
	20	3,554,072	344.0	10,330	1,603,832	257.2	6,236

The results above indicate that adding 8mg of rosiglitazone after mono-therapy failure with metformin remains a cost-effective option compared to adding sulphonylurea. Nevertheless, the incremental cost effectiveness ratios are significantly higher after the sensitivity analysis (Table 75 Vs Table 44)

- Obese patients uncontrolled on maximum dose of metformin. Comparing addition of rosiglitazone to addition of sulphonylurea and then switching to rosiglitazone:



**Table 76: Cost per QALY of switching from Met + SU to Met + Rosi using 8mg dose**

Time from diagnosis	Years from start of combination therapy	Undiscounted			Discounted		
		Costs	QALYs	ICER	Costs 6%	QALYs 1.5%	ICER
17.5	7.5	2,833,917	14.0	202,857	1,383,611	11.4	121,263
22.5	12.5	2,879,952	29.8	96,740	1,398,227	23.2	60,320
27.5	17.5	2,926,344	38.6	75,773	1,409,233	29.3	48,080
32.5	22.5	2,939,483	43.2	67,996	1,411,545	32.3	43,742
	20	2,932,914	40.9	71,666	1,410,389	30.8	45,807

The sensitivity analysis clearly demonstrates that adding 8mg of Rosiglitazone after metformin mono-therapy failure is not a cost-effective option compared to adding sulphonylurea and then switching to rosiglitazone. We observe that the incremental cost-effectiveness ratios have significantly changed after the variation in the rosiglitazone dosage (Table 76 Vs Table 46).

#### 4.12.4 Conclusions on the health economics of treatment with rosiglitazone in type 2 diabetes

- There is an inadequate exploration of uncertainty within the model. No sensitivity analysis was performed by the company on the variables that drive the model: treatment effects on insulin sensitivity and beta cell function, costs, glucose threshold. Furthermore, it was difficult for us to

perform sensitivity analysis on the treatment effects, as the exact relationship between insulin sensitivity and beta-cell function was unknown to us.

- Several sub-models are presented in the GSK model, which are built based on large databases. However, no information about the methods or diagnostics of the models was provided by the company.
- The baseline economic results for rosiglitazone indicate that rosiglitazone is a cost-effectiveness treatment for type 2 diabetes. Nevertheless, our sensitivity analysis has indicated that some of the scenarios are very sensitive to changes in key effectiveness variables.

The key economic results and their variations after the sensitivity analyses performed are summarised in the following table:

**Table 77: Summary of key economic results and sensitivity analyses (discounted cumulative values per 1,000 patients)**

<b>7.5 years after start of combination therapy</b>	<b>Comparison of Scenarios</b>	<b>S→I Vs S→S+R→I lean</b>	<b>S→I Vs S→S+R→I overweight</b>	<b>M→I Vs M→M+R→I</b>	<b>M→M+S→I Vs M→M+R→I</b>	<b>M→M+S→M+R→I Vs M→M+R→I</b>
<b>CENTRAL ESTIMATE</b>	Cost/QALY	Rosi dominates	Rosi dominates	Rosi dominates	9,972	11,857
	Cost/LYG	Rosi dominates	Rosi dominates	Rosi dominates	262,253	259,591
<b>SENSITIVITY ANALYSIS</b>	HbA1c threshold	Rosi dominates	Rosi dominates	Rosi dominates	3,937	24,962
	Insulin Sensitivity	Rosi dominates	Rosi dominates	Rosi dominates	Comparator dominates	Comparator dominates
	Beta Cell Function	Rosi dominates	Rosi dominates	Rosi dominates	Comparator dominates	Comparator dominates
	In-patient Costs	Rosi dominates	Rosi dominates	Rosi dominates	9,968	11,854
	Insulin Cost	999	859	1,715	11,070	12,401
	Rosiglitazone Dosage	-	-	1,558	17,389	121,263



#### 4.12.5 Comparison of the Takeda model and the GSK model.

##### **Table 78: Comparing the cost per LYG of the Takeda and GSK models**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

##### **Table 79: Efficacy of comparators in the two models**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

##### **Table 80: Cost/LYG of Pioglitazone using data inputs of the GSK model**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

#### 4.12.7 Conclusions

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

The results of the sensitivity analyses suggest that the cost per QALY of rosiglitazone is most sensitive to two variables; dosage and a change in the treatment effect i.e. effect of rosiglitazone on beta-cell function and insulin sensitivity (Table 77).

The cost per QALY ratio of rosiglitazone is most sensitive to a change in its treatment effect. In the central estimate provided by GSK, rosiglitazone is cost-effective in all scenarios, whether it is compared to metformin or sulphonylurea. However, if the effect of rosiglitazone on beta-cell function and insulin sensitivity is reduced so that the resulting HbA1c reduction is that of the higher confidence interval, the cost-effectiveness changes dramatically. In the two scenarios where rosiglitazone is compared to metformin and sulphonylurea combination therapy, the cost-effectiveness of rosiglitazone switches from being cost-effective to being dominated by the comparator strategy.

This suggests that small changes in the effect of rosiglitazone on beta-cell function and insulin sensitivity induce large changes in the cost per QALY ratios. Therefore there is a high level of uncertainty associated with the treatment effect of rosiglitazone. *Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.* As seen in Table 77, the cost per QALY ratio of rosiglitazone increase significantly if it is assumed that 100% of patients receive 8mg.

GSK did not perform any univariate or multivariate sensitivity analyses on the model. Furthermore, due to the complexity of the model it has not been possible within the rapid review

timescales to do a full multivariate analysis. The univariate sensitivity analyses that have been performed indicate that there is a wide degree of uncertainty, for example ranging from a cost effectiveness under £20,000 per QALY to being dominated, in the key scenarios under consideration.

The cost per QALY ratios presented in the GSK model suggest that Rosiglitazone therapy, combined with either metformin or sulphonylurea, is an economically attractive option. The current NICE guideline suggests that glitazone combination therapy should only be tried after metformin and sulphonylurea combination therapy has failed. However, the cost per QALY ratios presented in the GSK model suggest that it is potentially economically viable to use rosiglitazone combination therapy directly after failure of monotherapy with either metformin or sulphonylurea. However, since the baseline estimate of cost effectiveness is not robust to changes in the treatment effect and is reliant on the many assumptions included within the metabolic and long term economic models caution should be used in interpreting this baseline favourable result.

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

## 5. IMPACT ON THE NHS

There is a high level of uncertainty in the potential budgetary impact of the glitazones on the NHS, any estimates inevitably are based heavily on a series of assumptions, many of which cannot be justified easily.

It is thought that an estimated 800,000 people within England and Wales have type 2 diabetes.<sup>67</sup> This figure may be an underestimate as the King's Fund Report<sup>68</sup> of 1996 estimates that roughly two million people over the age of 16 in the UK suffer from Non-Insulin Dependent Diabetes Mellitus. Crudely weighting this prevalence of type 2 Diabetes in the UK to England and Wales alone<sup>69</sup> suggests that approximately 1.7 million people, diagnosed and undiagnosed, may suffer from the disease.

The UK Drug Information Pharmacists Group (UKDIPG)<sup>70,71</sup> makes the assumption that 50% of all diabetic patients currently on oral monotherapy are controlled inadequately. These estimates have a major impact on the number of patients eligible for treatment with the glitazones. The upper estimate of people potentially eligible for treatment with a glitazone in England and Wales is 212,000.

### *Pioglitazone*

A valid estimation of the costs to the NHS must include both the 30mg pioglitazone dose and also the lower 15mg dose. In the absence of any information to support an estimate of the breakdown of prescribing between doses, an assumption of a 50:50 split is just as valid as any other estimate. It should be noted in this regard that the economics of treatment with the 15mg dose have not been addressed within the economic submission.

The daily cost of pioglitazone is £1.32 for the 30mg dose and £0.95 for the 15mg dose.<sup>8</sup> The average annual cost per patient, therefore, is the average of the annual treatment at 15mg and at 30mg. This gives a figure of £414.28 for the estimated annual cost of pioglitazone. This is then multiplied by the number of eligible patients taking it in combination with sulphonylurea and metformin respectively. The resulting estimate of gross drug costs for pioglitazone in England and Wales, assuming all eligible patients are prescribed are as follows:

- P+S:                    £414.28 \* 34,700 people                    = £14,375,516
- P+M:                    £414.28 \* 40,000 people                    = £16,571,200
- Gross cost of pioglitazone in England and Wales                    = £30,946,716

The gross cost of pioglitazone should, however, be considered against potential savings in other available treatment options. When used in combination with sulphonylureas, the only alternative add on therapy considered within the Takeda submission<sup>29</sup> is acarbose, although this is not widely used within the UK. The only other intervention considered is to switch to intensive insulin therapy. When used in combination with metformin, the alternative add on therapies considered within the Takeda submission are acarbose and sulphonylureas. As discussed above, acarbose is not widely used within the UK. The maximum potential savings from the reduced usage of insulin and sulphonylureas are detailed below assuming that all patients using pioglitazone would have used one of these two alternative therapies (a potentially generous assumption) and that the average insulin daily dose saved is 60 units.



The key assumptions are:

- The proportion of eligible patients who receive treatment;
- The average saving in the use of insulin by patients who receive rosiglitazone;
- The average saving in the use of sulphonylurea by patients who receive rosiglitazone.

## 6. APPENDICES

### **Appendix 1 Electronic Bibliographic Databases Searched**

1. Cinahl
2. Cochrane Controlled Trials Register (CCTR)
3. Cochrane Database of Systematic Reviews (CDSR)
4. Database of Abstracts of Reviews of Effectiveness (DARE)
5. Embase
6. Health Technology Assessment (HTA) Database
7. Medline
8. NHS Economic Evaluations Database (NHS EED)
9. OHE Health Economic Evaluations Database (HEED)
10. PreMedline
11. Science Citation Index
12. Social Sciences Citation Index

## **Appendix 2 Other Sources Consulted**

1. Agency for Healthcare Research and Quality (AHRQ)
2. Aggressive Research Intelligence Facility (ARIF)
3. Association of British Clinical Diabetologists
4. Association of Diabetes Specialist Nurses
5. Aventis
6. Bandolier
7. British Dietetic Association
8. Canadian Co-ordinating Centre for Health Technology Assessment (CCOHTA)
9. CenterWatch Trials Register
10. Centre for Health Economics, University of York
11. Copernic
12. Current Controlled Trials (CCT)
13. Current Research in Britain (CRiB)
14. Department of Health
15. Diabetes Foundation
16. Diabetes UK
17. eBNF
18. Electronic Medicines Compendium
19. eGuidelines
20. European Agency for the Evaluation of Medicinal Products (EMA)
21. Food and Drugs Administration (FDA)
22. Google
23. Health Evidence Bulletins, Wales
24. Heart Disease and Diabetes Research Trust
25. International Network of Agencies for Health Technology Assessment (INAHTA) Clearinghouse
26. Index to Theses
27. Medlineplus Drug Information
28. MeReC
29. Medical Research Council (MRC) Funded Projects Database
30. National Assembly for Wales
31. National Guideline Clearinghouse (NGC)
32. National Research Register (NRR)
33. National Co-ordinating Centre for Health Technology Assessment (NCCHTA)
34. Organising Medical Networked Information (OMNI)
35. Primary Care Diabetes UK
36. Research Findings Register (ReFeR)
37. Royal College of Physicians
38. ScHARR Library Catalogue
39. Scottish InterCollegiate Guideline Network (SIGN)
40. Trent Working Group on Acute Purchasing
41. Turning Research into Practice (TRIP) Database
42. Wessex Development and Evaluation Committee (DEC) Reports
43. West Midlands Development and Evaluation Services (DES) Reports
44. World Health Organisation (WHO)

### **Appendix 3 Search Strategies Used in the Major Electronic Bibliographic Databases**

#### **CDSR and CCTR**

*2002 Issue 1*

*The Cochrane Library, Update Software (CD-ROM version)*

*Search undertaken April 2002*

- #1. GLITAZONE\*
- #2. THIAZOLIDINEDION\*
- #3. PPAR GAMMA AGONIST\*
- #4. PIOGLITAZONE\*
- #5. ACTOS
- #6. ROSIGLITAZONE\*
- #7. AVANDIA
- #8. TROGLITAZONE\*
- #9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

**Cinahl**

1982-2002

Ovid Biomed

Search undertaken April 2002

- 1 glitazone\$.af
- 2 thiazolidinedione.af
- 3 peroxisome proliferator activated receptor gamma agonist\$.tw
- 4 ppar gamma agonist\$.af
- 5 actos.af
- 6 1101025-46-8.rn
- 7 ad-4833.af
- 8 u-72107.af
- 9 pioglitazone\$.af
- 10 rosiglitazone\$.af
- 11 avandia.af
- 12 122320-73-4.rn
- 13 brl-49653.af
- 14 troglitazone\$.af
- 15 97322-87-7.rn
- 16 thiazole\$.ti
- 17 or/1-16
- 18 exp diabetes mellitus/  
diabet\$.tw
- 19 diabet\$.tw
- 20 or/18-19
- 21 17 and 20

**CRD Databases (NHS DARE, EED, HTA)**

*CRD Web site - complete databases*

*Search undertaken April 2002*

glitazone or thiazolidinedione or ppar gamma agonist or pioglitazone or actos or  
rosiglitazone or avandia or troglitazone/All fields

**Embase**

1980-2002

SilverPlatter WebSPIRS

Search undertaken April 2002

- #1 glitazone\*
- #2 thiazolidineione\*
- #3 peroxisome proliferator activated receptor gamma agonist\*
- #4 ppar gamma agonist\*
- #5 pioglitazone\*
- #6 actos
- #7 111025-46-8
- #8 ad-4833
- #9 u-72107
- #10 rosiglitazone\*
- #11 avandia
- #12 122320-73-4
- #13 brl-49653
- #14 troglitazone\*
- #15 97322-87-7
- #16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
- #17 explode 'diabetes-mellitus' / all subheadings
- #18 diabet\*
- #19 #17 or #18
- #20 #16 and #19

**HEED (Office of Health Economics Health Economic Evaluation Database)**

*CD ROM version*

*Search undertaken April 2002*

Search terms:

- glitazone\* or pioglitazone\* or rosiglitazone\* or avandia or actos or ppar gamma agonist\*

Fields searched:

- All data

**Medline**

1966-2002

Ovid Biomed

Search undertaken April 2002

- 1 glitazone\$.af
- 2 thiazolidinedione.af
- 3 peroxisome proliferator activated receptor gamma agonist\$.tw
- 4 ppar gamma agonist\$.af
- 5 actos.af
- 6 1101025-46-8.rn
- 7 ad-4833.af
- 8 u-72107.af
- 9 pioglitazone\$.af
- 10 rosiglitazone\$.af
- 11 avandia.af
- 12 122320-73-4.rn
- 13 brl-49653.af
- 14 troglitazone\$.af
- 15 97322-87-7.rn
- 16 thiazole\$.ti
- 17 or/1-16
- 18 exp diabetes mellitus/  
19 diabet\$.tw
- 20 or/18-19
- 21 17 and 20

**Science and Social Sciences Citation Index**

1981-2002

*Web of Science*

*Search undertaken April 2002*

Title=(glitazone\* or thiazolidinedione or ppar gamma agonist\* or actos or pioglitazone\* or rosiglitazone\* or avandia or troglitazone\*) and diabet\* not (rat or rats or mice or mouse); DocType=All document types; Languages=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years

## **Appendix 4 Economic Evaluations and Quality of Life Methodological Search Filters Used in Medline (Ovid) 1966-June 2002**

### **Economic evaluations**

- 1 economics/
- 2 exp "costs and cost analysis"/
- 3 economic value of life/
- 4 exp economics, hospital/
- 5 exp economics, medical/
- 6 economics, nursing/
- 7 economics, pharmaceutical/
- 8 exp models, economic/
- 9 exp "fees and charges"/
- 10 exp budgets/
- 11 ec.fs
- 12 (cost or costs or costed or costly or costing\$.tw
- 13 (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw
- 14 or/1-13

### **Quality of life**

- 1 exp quality of life/
- 2 quality of life.tw
- 3 life quality.tw
- 4 hql.tw
- 5 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
- 6 qol.tw
- 7 (euroqol or eq5d or eq 5d).tw
- 8 qaly\$.tw
- 9 quality adjusted life year\$.tw
- 10 hye\$.tw
- 11 health\$ year\$ equivalent\$.tw
- 12 health utilit\$.tw
- 13 hui.tw
- 14 quality of wellbeing\$.tw
- 15 quality of well being.tw
- 16 qwb.tw
- 17 (qald\$ or qale\$ or qtime\$.tw
- 18 or/1-17

## **Appendix 5 Correspondence with GSK**

*Information from the sponsor's submission was submitted in confidence to the National Institute for Clinical Excellence. This information was made available to the NICE Appraisals Committee but has been removed from this version of the report.*

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