New Medicine Recommendation
Metformin

For reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance and/or impaired fasting glucose, and/or increased HbA_{1c} who are:

- **at high risk for developing overt type 2 diabetes mellitus and**
- **still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months**

Recommendation: Green (as a second line treatment to intensive lifestyle-intervention)

Metformin[a] is recommended for the reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance and/or impaired fasting glucose, and/or increased HbA_{1c} who are:

- **at high risk for developing overt type 2 diabetes mellitus AND**
- **still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months OR**
- **are unable to participate in an intensive lifestyle-change programme.**

Summary of supporting evidence:

- Intensive lifestyle-intervention is the most effective treatment to prevent the development of type 2 diabetes, it also improves blood pressure and lipid control.
- The large and long-term **DPP** and **DPPOS** studies both demonstrate significantly reduced diabetes incidence in patients taking metformin who are at high risk of developing diabetes compared to control.
- Studies in China, Pakistan and India support the finding of the **DPP** and **DPPOS** regarding metformin efficacy in patients at risk of developing diabetes.
- Metformin has a long history of safe use in diabetic patients and no additional safety concerns were raised in any study regarding the use of metformin in prediabetic patients.
- Issues with long-term adherence to intensive lifestyle-interventions necessitate an alternate treatment option in those still progressing towards type 2 diabetes despite implementation of intensive lifestyle change.
- Although an initial cost burden is expected, economic analyses demonstrate the long-term cost-effectiveness of metformin and even indicate that cost savings may be possible.
- The other available pharmacological treatments for the prevention of progression to type 2 diabetes such as orlistat and acarbose are off-label uses of these medicines and there is less published evidence to support their use than for metformin. Also use of orlistat and acarbose for their licensed indications are associated with lack of adherence due to gastro-intestinal adverse effects.

[a] The product first licensed in the indication for which this review was conducted was Glucophage SR®. At the December meeting of the LMMG, the committee agreed to approve generic metformin in this indication based on immediate release metformin being the drug used to demonstrate efficacy.

Details of Review

Name of medicine (generic & brand name)**:** Metformin

Strength(s) and form(s): 500mg, 750mg and 1000mg prolonged release tablets

Dose and administration: The therapy should be initiated with one metformin 500 mg tablet once daily with the evening meal.

After 10 to 15 days, dose adjustment on the basis of blood glucose measurements is recommended (oral glucose tolerance test and/or fasting plasma glucose and/or HbA_{1c} values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets (2000 mg) once daily with the evening meal. [1]

BNF therapeutic class / mode of action

Biguanides / Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- increasing insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle
- delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters.

Licensed indication(s):

Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance and/or impaired fasting glucose, and/or increased HbA_{1c} who are:

- at high risk for developing overt type 2 diabetes mellitus and
- still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months

Treatment with metformin must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk.

Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so for medical reasons.

Proposed use (if different from, or in addition to, licensed indication above):

Course and cost:

Glucophage SR® tablets 500mg, 28=£2.66; 56=£5.32

Glucophage SR® tablets 750mg, 28=£3.20; 56=£6.40

Glucophage SR® tablets 1000mg, 28=£4.26; 56=£8.52

Annual cost per patient, if branded Glucophage SR® used and depending on dose, £35 - £111

Current standard of care/comparator therapies:

- Dietary and exercise lifestyle modifications
- Orlistat

Relevant NICE guidance:

NICE public health guideline (PH38): Type 2 diabetes: prevention in people at high risk

Background and context

Prediabetes, also commonly referred to as borderline diabetes or intermediate hyperglycaemia, is a metabolic condition and growing global problem that is closely tied to obesity. If undiagnosed or untreated, prediabetes can develop into type 2 diabetes; which whilst treatable is currently not fully reversible.

Prediabetes is characterised by the presence of blood glucose levels that are higher than normal but not yet high enough to be classed as diabetes. This was defined by a UK expert group as an HbA_{1c} of 42-47 mmol/ml (6.0-6.5%). [2] According to diabetes UK, around 7 million people in the UK are estimated to have prediabetes with the prevalence of prediabetes more than tripling in England between 2003 and 2011. [3] [4]

In July 2012, NICE published PH 38 "Type 2 diabetes: prevention in people at high risk" which outlined a series of recommendations for identifying and managing the risk of type 2 diabetes. For people confirmed as being at high risk of developing type 2 diabetes (a high-risk score and fasting plasma glucose (FPG) of 5.5–6.9 mmol/l or HbA_{1C} of 42–47 mmol/mol [6.0–6.4%]), the guideline recommends referral to a local, evidence-based, quality-assured intensive lifestyle change programme. In May 2017, Glucophage SR® (metformin) was licensed in the UK for reduction in risk or delay of onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance or impaired fasting glucose, and/or increased HbA1C who are at high risk for developing overt type 2 diabetes mellitus. The guideline was subsequently updated, stating that metformin is recommended as a treatment for adults at high risk of diabetes:

- Whose blood glucose measure (FPG or HbA_{1C}) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme.
- Who are unable to participate in lifestyle-change programmes because of a disability or for medical reasons.

NICE PH 38 recommends that eligible patients start with a low dose standard release metformin (e.g. 500mg once daily) and then increase gradually to 1500mg-2000mg daily. Modified-release metformin can be considered in those intolerant of standard metformin, although at the time of the guideline publication no metformin preparation was licensed for the prevention of type 2 diabetes. An initial treatment period of 6-12 months is recommended, monitoring FPG or HbA_{1C} levels at 3-month intervals and stopping metformin if no effect is seen. PH38 recommends standard release metformin as the pivotal diabetes prevention program (discussed below) used standard release metformin. The guideline acknowledges Glucophage SR is the only product currently licensed for the prevention of diabetes however other standard-release and modified-release metformin products may similarly extend their marketing authorisations in the future. [5]

Summary of evidence

Summary of efficacy data in proposed use:

The two largest clinical trials are the diabetes prevention program (DPP) measuring outcomes over an average of 2.8 years and an extension of this study called the diabetes prevention program outcome study (DPPOS) following patients up to year 15 of the study. A third phase assessing macrovascular outcomes runs until year 22 of the study and is currently on-going. [6]

DDP study

This was a multi-centre randomised double-blinded placebo-controlled clinical trial of 3234 non-diabetic patients with elevated FPG and post-load plasma glucose concentrations. Eligible patients were aged ≥25 years, had a BMI of ≥24 (≥22 in Asians), and a plasma glucose concentration of 95 to 125 mg per decilitre (5.3 to 6.9 mmol/L) in the fasting state (≤125 mg per decilitre in the American Indian clinics) and 140 to 199 mg per decilitre (7.8 to 11.0 mmol/L) two hours after a 75-g oral glucose load. Participants were excluded if they were taking medicines known to alter glucose tolerance or if they had illnesses that could seriously reduce their life expectancy or ability to participate in the trial. [7]

Participants were randomly assigned to the following groups:

- Metformin 850mg twice daily (initially once daily) plus standard lifestyle advice.
- Placebo twice daily plus standard lifestyle advice.

- An intensive program of lifestyle modifications (goals of ≥ 7% weight loss and ≥ 150 minutes of physical activity per week).

The predefined primary outcome of the trial was progression to diabetes as diagnosed by an annual oral glucose tolerance test (OGTT) or 6 monthly FPG test according to diagnosis criteria set out by the American Diabetes Association (FPG> 7.0 mmol/L or OGTT > 11.1mol/L) with a confirmatory test carried out 6 weeks later. Patients were also tested for diabetes if presenting to assessors with symptoms suggestive of diabetes. Secondary outcomes included glycaemic control, caloric intake and treatment adherence.

Primary outcome

The incidence of diabetes was significantly different between the patient groups with a 31% lower incidence (CI95% 17; 43, P<0.001) in the metformin group than the placebo group and a 58% lower incidence (CI95% 48; 66, P<0.001) in the intensive lifestyle- intervention group than in the placebo group. The study also demonstrated that the intensive lifestyle-intervention group had a 39% lower incidence of diabetes (CI95% 24; 51, P<0.001) than the metformin group. [7]

Secondary outcomes

In the first year there was a similar reduction in the mean FPG in the metformin and lifestyle-intervention groups whereas the values rose in the placebo group. The values rose in parallel in all three groups in the subsequent years. There was a similar trend for the HbA_{1c} values although the HbA_{1c} value for the metformin group was in between the values of those for the lifestyle-intervention group and the placebo group.

Treatment adherence was demonstrated by change in weight and physical activity in the lifestyle-intervention group and medication adherence in the metformin group. Of participants in the lifestyle-intervention group, 50% had achieved ≥7% weight loss at 24 weeks (38% at the most recent assessment) and 74% had achieved ≥150 minutes of physical activity per week (58% at the most recent assessment). The proportion of patients who took ≥80% of the prescribed study dose was 77% in the placebo group and 72% in the metformin group.

The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively (P<0.001). Daily energy intake decreased by a mean (±SE) of 249±27 kcal in the placebo group, 296±23 kcal in the metformin group, and 450±26 kcal in the lifestyle-intervention group (P<0.001). [7]

DPPOS study

The **DPPOS** study is the long term (10 year) open label study of the **DPP** participants. 88% of the eligible subjects from the **DPP** study were enrolled in **DPPOS**. Metformin treatment was continued in the original metformin group and placebo treatment was discontinued in the placebo group. All participants were offered intensive lifestyle-interventions due to the benefits noted in **DPP**. Therefore, **DDPOS** essentially compared metformin as an add-on treatment to intensive lifestyle-interventions.

As for the **DPP** study the primary outcome was incidence of diabetes and secondary outcomes were glycaemic control, change in weight, lipids, BP and microvascular endpoints. [6]

Primary outcome

For the latest analysis at year 15, crude diabetes incidence rates were 7, 5.7 and 5.2 cases per 100-person years respectively among the placebo, metformin and lifestyle groups, so the positive effects of the metformin and lifestyle interventions demonstrated in the **DPP** persisted despite an improvement in the placebo group following provision of the lifestyle-intervention in the unblinded phase.

The incidence of overt diabetes was reduced by 27% (HR 0.73 [CI95% 0.65; 0.83, P<0.0001]) in the intensive lifestyle group and by 18% (HR 0.82 [CI95% 0.72; 0.93, P<0.001]) in the metformin group, compared to placebo. [6]

Secondary outcomes

Mean weight loss was similar for patients originally randomised to the metformin and intensive lifestyle-intervention group. The BP and lipid benefits of the intensive lifestyle intervention in the **DPP** study disappeared over time in **DDPOS**, whereby improvements in BP and lipid parameters were similar across all treatment groups by the end of the **DDPOS** follow up period. An aggregate microvascular endpoint comprised of nephropathy, retinopathy and neuropathy measures did not demonstrate a significant difference between treatment groups in the total cohort after 15 years follow up [6]

The Indian Diabetes Prevention Programme (IDPP) [8]

This randomised, controlled trial of 531 patients with impaired glucose tolerance differed from the **DPP** trial in that it was not blinded and placebo-controlled, and the intensive lifestyle-intervention and metformin were evaluated separately and in combination. Patients only undertook 30 minutes of daily exercise if they were not already engaged in physical labour or regular exercise. Relative to the DPP study, a lower metformin dose of 500mg twice daily (increased from initial 250mg twice daily) was used and the **IDPP** continued for 2.5 years. The primary outcome was development of diabetes indicated by an FPG >7.0mmol/L and/or an OGTT > 11.1 mmol/L.

Similar significant reductions in the risk of diabetes were observed in the metformin (HR 0.651 [CI95% 0.27; 1.04, P=0.029]) and intensive-lifestyle intervention group (HR 0.623 [CI95% 0.23; 1.02, P=0.018]) compared to the control group (who only received standard healthcare advice). No additional benefit was observed in patients receiving the combined intensive-lifestyle intervention and metformin (HR 0.629 [CI95% 0.23; 1.03, P= 0.022]).

Other efficacy data:

Additional studies of metformin in diabetes prevention

Two smaller randomised studies demonstrated a significant effect of metformin on diabetic risk reduction in Chinese subjects with IGT during one year of treatment, and in Pakistani subjects with IGT during 18 months of treatment. As in the IDPP study no additional benefit was demonstrated when metformin was combined with intensive-lifestyle interventions. [9] [10]

Supportive studies for cardiovascular endpoints

The public assessment report for Glucophage SR® tablets includes further evidence from 4 large prospective studies carried out in Europe which assessed cardiovascular mortality rates in patients deemed to be at high risk of developing diabetes. Each study supported the hypothesis that patients at higher risk of developing diabetes as defined by FPG or OGTT were at increased risk of all-cause mortality and cardiovascular mortality. The assessment report states that these findings have been generally supported by other studies in the US, Asia and Australia. [6]

Summary of safety data:

The most common side effects of metformin are mild to moderate gastrointestinal adverse events such as diarrhoea, nausea and vomiting, abdominal pain and decreased appetite. These effects are most common upon treatment initiation and can be minimised by starting metformin at a low dose and titrating the dose carefully. A full list of side effects listed in the SPC are shown in the table below.

MedDRA system organ class	Very common (>1/10)	Common (≥1/100)	Very Rare (<1/10,000)
Metabolism and nutrition disorders			Lactic acidosis, decrease in vitamin B12 absorption (on long term use)
Nervous system disorders		Taste disturbance	
Gastrointestinal disorders	Nausea, vomiting diarrhoea, abdominal pain, loss of appetite		
Hepatobiliary disorder			LFT abnormalities, hepatitis
Skin and subcutaneous tissue disorders			Erythema, pruritus, urticaria

Serious side effects with metformin are very rare, although the association of metformin with lactic acidosis is described in the SPC. This occurs primarily in patients with renal impairment or cardiovascular disorders which may cause accumulation of metformin. For that reason, metformin is contraindicated in patients with a creatinine clearance of <30mL/min, recent myocardial infarctions or decompensated heart failure. Dose reductions are necessary in patients with a moderate degree of renal impairment.

Strengths and limitations of the evidence:

Strengths

- The large and long-term **DPP** and **DPPOS** studies both demonstrate significantly reduced diabetes incidence compared to control in patients taking metformin who are at high risk of developing diabetes.
- Studies in China, Pakistan and India support the finding of the **DPP** and **DPPOS** regarding metformin efficacy in patients at risk of developing diabetes.
- Metformin has a long history of safe use in diabetic patients and no additional safety concerns were raised in any study regarding the use of metformin in prediabetic patients.
- Various cost-effective analyses indicate that metformin with standard lifestyle advice may be more cost effective than intensive-lifestyle modifications.
- Although the **DPP** and **DPPOS** were not adequately powered to detect subgroup treatment differences the authors stated that metformin appears to work more effectively in younger patients with higher BMIs and baseline blood glucose values, as well as patients with a history of gestational diabetes.
- The UKPAR states that "overall there is good evidence to link prediabetes to cardiovascular disease". [6]
- A gradual progressive weight gain was observed in the intensive lifestyle-intervention group indicating the practical difficulties of adherence to this intervention.

Limitations

- No studies have been carried out in a European population assessing the effectiveness of metformin in preventing diabetes.
- Some of the trials supporting the **DPP** and **DPPOS** study may have been biased by lack of blinding, placebo and participant selection.
- The only other pharmacological treatment mentioned in the NICE public health guideline for the prevention of diabetes is orlistat, however no comparative studies of metformin and orlistat have been undertaken.
- In studies where metformin and intensive lifestyle-intervention were assessed alone and in combination, no reduction in diabetes incidence was observed in the combination intervention compared to either metformin or intensive lifestyle interventions alone.
- In the **DPPOS** study only 88% of eligible subjects were enrolled from the **DPP** study phase which may have biased the participant selection.
- Allowing all patients (including those on metformin) access to intensive lifestyle-intervention in the DPPOS phase of the trial has placed limitations on the interpretation of the effectiveness of metformin.
- There were different rates of compliance with the lifestyle interventions across the study groups in the **DPPOS** part of the study which may have affected the results.
- Although cardiovascular benefits of metformin in a prediabetic population are thought likely, uncertainty will remain until the macrovascular outcomes data from the **DPPOS** study is available (expected 2021).
- The dose of metformin varied across different trials, leading to less reliable comparisons of outcomes data across the trials.
- Metformin is licensed only when lifestyle modifications are continued (unless the patient is unable to do so for medical reasons), therefore the cost of standard lifestyle intervention must be added to the cost of metformin treatment.

Summary of evidence on cost effectiveness:

Two economic analyses have been undertaken using data from the **DPP** study comparing the cost effectiveness of metformin or intensive lifestyle intervention for diabetes prevention in patients with impaired glucose tolerance. One of the economic analyses was carried out from the prospective of the US health system over a ten-year timespan [11] and the other was from the prospective of various health economies including the UK over the lifespan of a patient. [12]

The conclusion of both economic analyses was that metformin treatment was cost-saving except in the case of the UK health economy where metformin was judged to incur additional costs although highly cost-effective compared to standard lifestyle advice. Both economic evaluations found metformin to be

more cost-effective than intensive lifestyle intervention. Both sets of authors concluded that the use of either intensive lifestyle interventions or metformin to prevent incidence of diabetes represented value for money.

Prescribing and risk management issues:

A patient's renal function should be checked before starting treatment, and then twice yearly thereafter (more often if patients are older or if deterioration is suspected).

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Glucophage SR® tablets	500 to 2000mg daily	£2.66 to £8.52 (depending on strength and pack size)	£35 - £111
Orlistat® 120mg capsules	One capsule three times daily at mealtimes	£13.96	£182
Costs based on MIMS list prices August 2017. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

Metformin must be used in conjunction with lifestyle modifications, unless the patient is unable to participate in a lifestyle modification intervention for medical reasons. The cost of commissioning standard lifestyle modifications rather than an intensive lifestyle-interventions must be considered in addition to the cost of metformin treatment. According to the NICE public health guideline for the prevention of diabetes, the efficacy of metformin treatment should be monitored using a person's fasting plasma glucose or HbA_{1c} levels at 3-month intervals for up to 12 months. Therefore monitoring costs need to be considered within the total cost of the metformin treatment.

Productivity, service delivery, implementation:

Screening for diabetes would be expected to take place primarily in a community setting by staff delivering the NHS Health Check program, community pharmacists, dental surgeries and opticians. For patients judged to be at risk of diabetes based on a validated risk-assessment questionnaire a blood test should be offered by the GP practice to check either FPG or HbA_{1c}.

Anticipated patient numbers and net budget impact:

Using data collected by the Health Survey for England in 2011, 35.3% of individuals aged 16 years and older have prediabetes defined as a HbA_{1c} of between 5.7% and 6.4%. [4]

NICE has produced a costing template for the prevention of diabetes using an intensive lifestyle-intervention program that can be adjusted to reflect the Lancashire population. This template takes into account the number of people already diagnosed with type 2 diabetes/prediabetes, costs that will already be covered by the NHS Health Check program and the likely demographics of patients who may be tested for diabetes. Based on these assumptions, NICE projects a target population of 674,859 in the Lancashire and Morecambe Bay Health Economy. The number of the target population extrapolated to be offered an intensive lifestyle intervention is **52,168.** NICE predicts an intervention uptake of 32% leading to **17,197** patients receiving the intensive lifestyle intervention at a cost of **£1,153,362**. [5]

The template indicates that the intervention will produce short term non-recurrent savings of £443,281 and annual recurrent savings of £4,915. Long term savings are excluded from the template model and difficult to accurately predict. It would be expected that when all these savings are accounted for, the net cost of the intervention would be significant lower than **£1,153,362**.

The licensed indication for Glucophage SR® tablets states that patients may use Glucophage SR® tablets if they are still progressing towards type 2 diabetes mellitus despite implementation of intensive

lifestyle change for 3 to 6 months. [1] The **DPP** study measured adherence to weight and exercise goals as a measure of overall treatment adherence to intensive lifestyle-intervention and found 50% of patients were unable to meet their weight and exercise goals. [7]

Assuming that the costs of medical consultations, diagnosis and monitoring are equal, the additional annual cost of metformin treatment is **£35-£111** (depending on dose) and the additional annual cost of an intensive lifestyle-intervention is **£61-£65** (depending on the patient cohort).

To treat 8,599 patients (50% of original uptake) with metformin who had failed on the intensive lifestyle-intervention would incur an additional annual cost of **£300,965 to £954,489** across the Lancashire and Morecambe Bay health economy.

Innovation, need, equity:

Glucophage SR® is the first licensed pharmacological treatment for the prevention of diabetes in patients at high risk of developing diabetes. Previously, off-label use of generic metformin was recommended in the NICE public health guideline as a potential treatment option to prevent progression to diabetes in at risk patient cohorts. [5]

The cost of using Glucophage SR® in place of generic metformin will generate a short term economic burden on health budgets. Based on current GMC guidelines it is likely that prescribers wishing to prescribe metformin to prevent development of diabetes in at risk patients will prescribe Glucophage SR® to offer a licensed treatment option.

Despite the increased short-term costs of using Glucophage SR® in the prevention of diabetes, several economic analyses indicate that this treatment is likely to be highly cost-effective or even cost-saving in the long-term, based on the reduced costs of treating diabetes and diabetic complications. [11] [12]

References

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Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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