

COMPASS Therapeutic Notes on the Newer Drugs used in the Management of Type 2 Diabetes Mellitus

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<i>Glossary of terms</i>	
DPP-4	Dipeptidyl peptidase-4
GLP	Glucagon-like peptide
HbA _{1c}	Glycosylated haemoglobin
MHRA	Medicines and Healthcare Regulatory Authority
SMBG	Self-monitoring of blood glucose
TZDs	Thiazolidinediones

- **Successful completion of the assessment questions at the end of this issue will provide you with 2 hours towards your CPD/CME requirements.**
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- **Pharmacists should enter their MCQ answers at www.nicpld.org**

Introduction and Background

It is important to bear in mind that glycaemic control in type 2 diabetes is just one aspect of an overall management plan that encompasses effective treatment of hypertension and dyslipidaemia,¹⁻⁴ both commonly encountered in patients with type 2 diabetes and are regarded as important modifiable risk factors for atherosclerosis, the principal cause of premature mortality.

A previous edition of COMPASS Therapeutic Notes (April 2007) detailed the cardiovascular aspects of type 2 diabetes.

This guidance has been written to inform prescribers and others of the “newer” hypoglycaemic agents being used in the management of type 2 diabetes. It is not intended to be a guide on the overall management of the condition. Readers are directed to guidance already available through NICE or to guidance issued by specialists locally.

management of hyperglycaemia in type 2 diabetes have broadly been limited to metformin, sulphonylureas and insulin therapy.

Targets

- The **Quality and Outcomes Framework (QOF)** glycaemic target requires 50% of patients to achieve HbA_{1c} < 7%.
- The **NICE guidance**⁹ embraces the newer agents for type 2 diabetes and allows glycaemic control to be tailored to individual patients without personal or professional constraint. At the same time there is clear advice to discontinue treatment in the absence of a “measurable” response, to prevent indiscriminate use. The NICE guidance continues to recommend an HbA_{1c} of 6.5% as a threshold for initiating or up-titrating therapy during the early stages of type 2 diabetes, while 7.5% remains the trigger for triple therapy. In general, NICE continue to recommend metformin as the first-line and a sulphonylurea as second-line therapy.

Recently, there has been much debate

about the necessity or harm of tight glycaemic control. This is an area of rapidly evolving evidence and, as yet, remains unclear.

Hypoglycaemic agents

When thought of simply, there are three ways in which antidiabetic agents work toward improving glycaemic control:

1. increasing insulin production
2. increasing insulin action
3. decreasing insulin need

See **Table ONE**.

Prescribing Note: “Black triangle” agents

The symbol “▼” identifies newly licensed medicines that are intensively monitored by the MHRA. For medicines showing this symbol, the MHRA asks that **all** suspected reactions are reported through the Yellow Card Scheme.

Until recently, the options for the

Table ONE: Agents used in Management of Type 2 Diabetes⁵⁻⁸

Class	Alternative names	Examples	Principle mode of action
Sulphonylureas		Gliclazide, glibenclamide, glipizide, glimepiride	<ul style="list-style-type: none"> • Stimulate insulin production (act 12-24 hours) • Mean reduction in HbA_{1c} = 1% to 1.5%
Postprandial glucose regulators	Insulin secretagogues Meglitinides Meglitinide analogues	Repaglinide Nateglinide	<ul style="list-style-type: none"> • Stimulate insulin production (act < 6 hours) • Mean reduction in HbA_{1c} = 0.5% to 1%
Biguanides		Metformin	<ul style="list-style-type: none"> • Counters insulin resistance (especially decreases hepatic glucose output) • Mean reduction in HbA_{1c} = 1% to 1.5%
Thiazolidinediones	“glitazones” TZDs PPAR-gamma agonists	Pioglitazone ▼ Rosiglitazone	<ul style="list-style-type: none"> • Insulin sensitisers, which act by lowering insulin resistance in peripheral tissues • Mean reduction in HbA_{1c} = 0.5% to 1.5%
Alpha-glucosidase inhibitor	Disaccharidase inhibitors	Acarbose	<ul style="list-style-type: none"> • Slows down rate of carbohydrate digestion. • Mean reduction in HbA_{1c} = 0.5% to 1%
Dipeptidyl peptidase-4 inhibitors	“gliptins” DPP-4 inhibitors	Sitagliptin ▼ Vildagliptin ▼ Saxagliptin ▼	<ul style="list-style-type: none"> • Stimulate insulin production • Suppress glucagon secretion • Mean reduction in HbA_{1c} = 0.5% to 1%
Incretin mimetic	Glucagon-like peptide-1 receptor agonists GLP-1 receptor agonists	Exenatide^a ▼ Liraglutide^a ▼	<ul style="list-style-type: none"> • Stimulate insulin production • Suppress glucagon secretion • Slow gastric emptying • Promote satiety • Mean reduction in HbA_{1c} = 0.5% to 1%

Note: those classes in **bold** are included in this review.
^a Administered parenterally

Table TWO: Comparative costs of the newer hypoglycaemic agents

Agent	Daily Dose	Cost of one year's treatment*
Pioglitazone	15 to 45 mg	£171.00 to £443.52
Rosiglitazone	4 to 8 mg	£240.00 to £360.00
Saxagliptin	5 mg	£379.20
Sitagliptin	100 mg	£399.12
Vildagliptin	50 to 100 mg	£190.56 to £381.12
Exenatide	5 to 20 mcg	£818.88
Liraglutide	0.6 to 1.8 mg	£470.88 to £1412.64
Nateglinide	180 to 540 mg	£272.52 to £310.56
Repaglinide	1.5 to 16 mg	£141.12 to £376.32

* based on prices in BNF59, March 2010

Table THREE: New Units for HbA_{1c}

From June 2009 people with diabetes should be having their HbA _{1c} measurements reported in "millimoles HbA _{1c} per mol of unglycosylated haemoglobin (mmol/mol)" as well as by the customary percentage. The old and new measurements are both being used for the first two years of the change, until May 2011 when people with diabetes will receive their HbA _{1c} measurements as mmol/mol only.	Comparative HbA _{1c} values	
	Old %	NEW mmol/mol
	6.0	42
	6.5	48
	7.0	53
	7.5	59
	8.0	64
	9.0	75
	10.0	86

Thiazolidinediones

Includes:

- Pioglitazone (Actos® ▼)
- Pioglitazone + metformin (Competact® ▼)
- Rosiglitazone (Avandia®)
- Rosiglitazone + metformin (Avandamet® ▼)

Mode of action

Thiazolidinediones act at the level of the genome, modifying the transcription of a number of genes that regulate insulin action and lipid metabolism.

Thiazolidinediones are ligands for peroxisome proliferator-activated receptor gamma (PPAR-gamma).¹⁰ The PPAR-gamma receptors are located in the nucleus of the cell and their activation by thiazolidinediones improves insulin action to increase glucose uptake in muscle and suppress hepatic glucose output.

Efficacy of the thiazolidinediones

Addition of rosiglitazone or pioglitazone to the treatment schedule of patients whose glycaemic control with a sulphonylurea or metformin is suboptimal has resulted in reductions in HbA_{1c} of around 0.5 – 1.5%.¹¹

Pharmacokinetics

Rosiglitazone and pioglitazone are rapidly, and nearly completely absorbed (1-2 hours to peak concentration), although absorption is slightly delayed when taken with food. Both agents are extensively metabolised by the liver.

Thiazolidinediones – monitoring requirements

There have been rare reports of hepatocellular dysfunction during post-marketing experience with rosiglitazone and pioglitazone.^{12,13} Therefore, liver enzymes should be checked prior to the initiation of therapy with a thiazolidinedione (a thiazolidinedione should not be started in patients with increased baseline liver enzymes or with any evidence of liver disease).^{12,13} Liver enzymes should be checked every 2-6 months for the first year, then annually in anyone on a glitazone. If ALT levels are increased to 3 times the upper limit of normal during glitazone therapy and remain elevated, therapy should be discontinued.^{12,13}



CPD into action

► Consider carrying out an audit of patients in your practice who are on rosiglitazone or pioglitazone and whether or not they have been having annual LFTs checked.

► Consider carrying out an audit of patients who have been on a thiazolidinedione for at least six months. Has their HbA_{1c} come down by at least 0.5%? If not, consider discontinuing the thiazolidinedione and/or seeking specialist advice.

What are the most common side-effects of thiazolidinediones?

Rosiglitazone and pioglitazone are generally well tolerated but have been linked to weight gain, fractures and cardiovascular adverse effects:

Weight gain

In trials with rosiglitazone and pioglitazone, there was evidence of dose-related weight gain,¹²⁻¹⁴ usually 3-4 kilograms in the first six months of therapy. Therefore weight should be closely monitored, given that it may be attributable to fluid retention, which may be associated with cardiac failure.

Heart failure

There is consistent evidence that rosiglitazone and pioglitazone can cause weight gain and fluid retention, which can lead to new or worsening heart failure that can be fatal.^{15,16} The RECORD study reported in 2009¹⁷ and confirmed that therapy which includes rosiglitazone substantially increases the risk of heart failure.

Ischaemic heart disease

In addition to concerns about heart failure, rosiglitazone may increase the risk of acute MI.^{15,18}

A 2009 study explored the relative cardiovascular safety of rosiglitazone and pioglitazone in a population of approximately 1.6 million older patients.¹⁹ This found that pioglitazone was associated with a lower risk of adverse cardiovascular events and death than was rosiglitazone.

Fracture-risk

The fracture side-effect with thiazolidinediones was first discovered at the end of 2006 in the ADOPT¹⁴ study. Although originally thought that the increased risk of fracture occurred mainly in women,²⁰ a later study found glitazones were associated with an increased risk of fractures in both men and women.²¹

Contraindications to the use of thiazolidinediones

Both pioglitazone and rosiglitazone are contraindicated in patients with:^{12,13}

- cardiac failure or history of cardiac failure (NYHA class I to IV)^{12,13}
- hepatic impairment^{12,13}
- increased risk of fractures.^{22,23}

In addition, rosiglitazone is contraindicated in patients with a history of an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI).

What is the place of thiazolidinediones in therapy?

NICE suggests **adding** rosiglitazone or pioglitazone to metformin as **second-line therapy** (instead of a sulphonylurea) when control of blood glucose remains or becomes inadequate if:⁹

- The person is at significant risk of hypoglycaemia or its consequences. Or
- A person does not tolerate a sulphonylurea or a sulphonylurea is contraindicated.

The thiazolidinediones also have a role as **third-line therapy** and can be **added** to metformin plus a sulphonylurea when control of blood glucose remains or becomes inadequate.

Therapy with a thiazolidinedione should be continued only if the person has had a beneficial metabolic response (a reduction of at least 0.5% in HbA_{1c} in six months).⁹



Prescribing Note: Thiazolidinediones

► It is important to remember that after starting thiazolidinediones, there may be a delay of 6-8 weeks before their full effect is seen due to their mode of action inducing transcription of genes that regulate proteins involved in insulin action and lipid metabolism.

What are thiazolidinediones licensed for?

Rosiglitazone or pioglitazone are licensed in type 2 diabetes:^{12,13}

- As **monotherapy** in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate.
- As **dual therapy** in combination with:
 - Metformin (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.
 - A sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient

glycaemic control despite monotherapy with a sulphonylurea

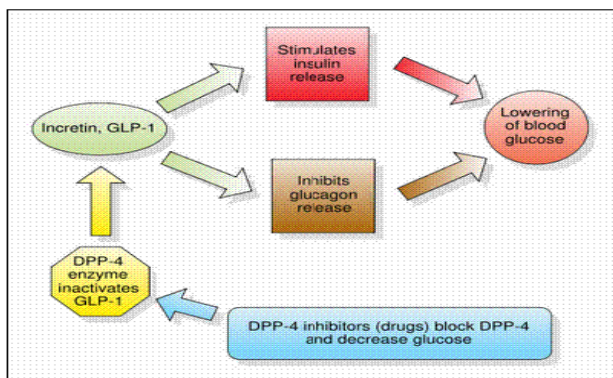
- As **triple oral therapy** in combination with metformin and a sulphonylurea in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
- Additionally, pioglitazone is also licensed for combination with insulin in type 2 diabetes.¹³

Rosiglitazone is usually initiated at 4 mg/day. This dose can be increased to 8 mg/day after eight weeks if greater glycaemic control is required.¹² Rosiglitazone may be given once or twice a day and may be taken with or without food.¹² Pioglitazone tablets are taken once daily with or without food. Pioglitazone may be initiated at 15

milligrams or 30 milligrams once daily. The dose may be increased in increments up to 45 milligrams once daily.¹³

The therapeutic response varies markedly between patients and it can be difficult to predict those most likely to respond. If no effect is observed after three months it is appropriate to consider the patient as a non-responder and to stop treatment. Rosiglitazone and pioglitazone can be used in the elderly, provided there are no contraindications. Both drugs can be used in mild to moderate renal impairment, although the potential for oedema is a concern.

Incretin-based therapies – general introduction



glucose administration.²⁵ This difference is known as the *incretin effect*.

The two gut peptides accounting for most of the incretin effect are:²⁶

- GLP-1 (Glucagon-like peptide 1) – synthesised by cells in the distal small bowel and colon.
- GIP (Glucose-dependent

insulinotropic peptide) – secreted by duodenal and proximal jejunal cells. Plasma concentrations of GIP and GLP-1 are low during fasting, but rise within minutes of food ingestion.²⁷ Incretins interact with specific receptors on β -cells of the pancreas and thereby stimulate insulin secretion. In addition,

GLP-1 decreases pancreatic secretion of glucagon (a hormone that augments glucose production by the liver). GLP-1 also slows gastric emptying and may have an action as an appetite suppressant. GIP and GLP-1 are rapidly degraded in the circulation by the enzyme dipeptidyl peptidase-4 (DPP-4).

In someone with type 2 diabetes, GLP-1 levels are reduced, while GIP action is defective or absent. Thus the blunted incretin response in type 2 diabetes is due to both impaired secretion of GLP-1 and defective activity of GIP.

Two classes of therapies target the incretin system:

- DPP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin) - these rely on production of endogenous GLP-1 and act by reducing its turnover.
- GLP-1 agonists (exenatide, liraglutide) – these mimic the action of GLP-1 and are not degraded by DPP-4.

What are “incretins” and what is the “incretin effect”?

Incretins are gastrointestinal hormones released in response to meals to increase insulin secretion.²⁴ It has been observed that insulin secretion is substantially increased in response to oral glucose, compared to intravenous

insulinotropic peptide) – secreted by duodenal and proximal jejunal cells. Plasma concentrations of GIP and GLP-1 are low during fasting, but rise within minutes of food ingestion.²⁷ Incretins interact with specific receptors on β -cells of the pancreas and thereby stimulate insulin secretion. In addition,

Gliptins (Dipeptidyl peptidase-4, DPP-4, inhibitors)

Includes:

- Saxagliptin (Onglyza[®]▼)
- Sitagliptin (Januvia[®]▼)
- Vildagliptin (Galvus[®]▼)
- Vildagliptin + metformin (Eucreas[®]▼)

As explained above, the knowledge that the incretins GLP-1 and GIP are rapidly inactivated by DPP-4 led to the development of agents that would inhibit DPP-4, thereby prolonging the biological half-lives of endogenous incretins and increasing their effectiveness. The first DPP-4 inhibitor to come to the UK market was sitagliptin in 2007 and subsequently vildagliptin in 2008 and saxagliptin in 2009.^{28,29}

How are the gliptins administered?
See **Table FOUR**.

How effective are the gliptins?

The DPP-4 inhibitors are modestly effective glucose-lowering drugs. Average HbA_{1c} reductions range

between 0.6% and 0.8% compared with placebo.³⁰⁻³² When compared with other hypoglycaemic agents, the efficacy of DPP-4 inhibitors has efficacy marginally lower than metformin³³ but similar to rosiglitazone³⁴ and glipizide.³⁵ Greater reductions have been observed in patients with higher baseline HbA_{1c} levels.^{31,35-37}

How do these agents affect body weight?

The gliptins have been shown not to alter body weight.^{6,30,38}

What are the adverse effects of the gliptins?

Gliptins have good tolerability and very few side-effects. However, the following have been associated with use of the gliptins:

Hepatic dysfunction

Rare cases of hepatic dysfunction (including hepatitis) have been reported

with vildagliptin.^{39,40} In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of vildagliptin therapy is recommended.³⁹

Implications of long-term inhibition of DPP-4

In addition to their role in the degradation of GLP-1 and GIP, dipeptidyl peptidase also appear to play important roles in haematologic and immune cells.⁴³ Accordingly, concern has been raised regarding the long-term implications of DPP-4 inhibition. The members of this class that are currently available have reasonably high selectivity for DPP-4, and few adverse effects in humans have been demonstrated thus far.^{30-32,44,45}

Other adverse effects

- Idiosyncratic reactions of vildagliptin include cold/flu-like symptoms, headache and dizziness, peripheral oedema, arthralgia and infections.^{25,46,47}
- Sitagliptin has been associated with an increased risk for urinary tract infections, headache, nasopharyngitis and upper-respiratory tract infection.^{48,49}
- Saxagliptin use is linked with upper respiratory infections, urinary tract infections, gastroenteritis, sinusitis, nasopharyngitis, headache and vomiting.

Interactions with gliptins

Vildagliptin and sitagliptin have a low potential for drug interactions.^{39,42} They do NOT interact with metformin, rosiglitazone, ciclosporin, digoxin, simvastatin, warfarin, or oral contraceptives.^{39,42}

Saxagliptin is metabolised to an active metabolite mainly by CYP3A4/5. Strong inhibitors of CYP3A4, such as clarithromycin, can increase serum concentrations of saxagliptin. Rifampicin, a strong inducer of CYP3A4, has decreased serum concentrations of saxagliptin, but not those of its active metabolite.^{41,50}

What does NICE recommend with regard to using DPP-4 inhibitors?

(At the time the NICE guidelines were written, only two DPP-4 inhibitors were available: vildagliptin and sitagliptin. However, it seems reasonable to extrapolate their recommendations to include saxagliptin also.)

NICE suggests that DPP-4 inhibitors have a role as second or third-line agents in the management of type 2 diabetes.⁹

- Consider adding a DPP-4 inhibitor instead of a sulphonylurea as **second-line therapy** to metformin when

control of blood glucose remains or becomes inadequate if the person:

- is at significant risk of hypoglycaemia or its consequences
- does not tolerate a sulphonylurea or a sulphonylurea is contraindicated.

• Consider adding sitagliptin as **third-line therapy** to metformin plus a sulphonylurea when control of blood glucose remains or becomes inadequate and insulin is unacceptable or inappropriate. Sitagliptin is currently the only DPP-4 inhibitor licensed for this indication.

NICE recommends that therapy with a DPP-4 inhibitor should be continued only if therapy has resulted in a reduction of at least 0.5% in HbA_{1c} in six months.⁹



CPD into action

► Consider carrying out an audit of patients in your practice who have been on a DPP-4 inhibitor for at least six months. Has their HbA_{1c} come down by at least 0.5%? If not, consider discontinuing the DPP-4 inhibitor and/or seeking specialist advice.

GLP-1 analogues (exenatide ▼, liraglutide ▼)

Exenatide was the first of a new class of compounds known as GLP-1 analogues or "incretin mimetics". Exenatide (Byetta® ▼) became available in the UK in May 2007. The second agent in this class, liraglutide (Victoza® ▼) was launched in the UK in July 2009.⁵¹ Liraglutide has greater homology with human GLP-1 than exenatide (97% versus 53%).⁵²

How do GLP-1 analogues work?

As explained previously, GLP-1 is a hormone secreted by the intestines during food absorption. Exenatide and liraglutide are analogues of GLP-1, they act to potentiate insulin secretion, inhibit secretion of glucagon, slow gastric emptying and promote gastric satiety. In patients with diabetes, this results in modest lowering of fasting glucose and marked reduction of postprandial glucose levels.

What is exenatide licensed for?

Exenatide is indicated for treatment of type 2 diabetes in combination with metformin and/or a sulphonylurea in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.⁵³

What is liraglutide licensed for?

Liraglutide is licensed for the treatment of adults with type 2 diabetes to achieve glycaemic control.⁵⁴

- In combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated doses of metformin or sulphonylurea.

- In combination with metformin *and* a sulphonylurea or metformin *and* a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

How is exenatide administered?

Exenatide is delivered by twice daily subcutaneous injection using a pre-filled pen device. Exenatide therapy should be initiated at a dose of 5 micrograms twice daily, for at least one

month in order to improve tolerability. The dose can then be increased to 10 micrograms twice daily to further improve glycaemic control. Doses higher than 10 micrograms twice daily are not recommended.⁵³ Exenatide can be administered at any time within the 60 minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). Exenatide **should NOT be administered after a**

Table FOUR: Using the gliptins

Agent	Indication	Dose
Saxagliptin ⁴¹	As add-on therapy, in adult patients with type 2 diabetes, in combination with metformin, or a sulphonylurea, or a thiazolidinedione.	5 milligrams once daily, with or without food
Sitagliptin ⁴²	As monotherapy in patients inadequately controlled by diet and exercise alone and when metformin is contraindicated or not tolerated. (Sitagliptin is the only DPP-4 inhibitor licensed as monotherapy). As dual therapy with metformin or a sulphonylurea or a thiazolidinedione. As triple therapy with metformin + a sulphonylurea, or metformin + thiazolidinedione.	100 milligrams once daily, with or without food.
Vildagliptin ³⁹	As dual oral therapy in combination with: ³⁹ • Metformin, or • A sulphonylurea, or • A thiazolidinedione.	When used in combination with metformin or a thiazolidinedione, vildagliptin 50 milligrams is given twice daily. When used in combination with a sulphonylurea, the recommended dose of vildagliptin is 50 milligrams once daily. Vildagliptin can be taken with or without food.

Note: sitagliptin should be avoided if eGFR less than 50ml/minute/1.73m³

meal. If an injection is missed, the treatment should be continued with the next scheduled dose.⁵³ Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.⁵³ The dose of exenatide does not need to be adjusted on a day-to-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas.⁵³

How is liraglutide administered?

Liraglutide is supplied in a pre-filled pen device.⁵⁴ Liraglutide is given once daily, independent of meals, by subcutaneous injection into the abdomen, thigh or upper arm.⁵⁴

To improve gastrointestinal tolerability, the starting dose is 0.6 milligrams liraglutide daily. After at least one week, the dose should be increased to 1.2 milligrams. Some patients are expected to benefit from an increase in dose from 1.2 milligrams to 1.8 milligrams and based on clinical response, after at least one week the dose can be increased to 1.8 milligrams to further improve glycaemic control. Daily doses higher than 1.8 milligrams are not recommended. Liraglutide can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged. Liraglutide can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When liraglutide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.⁵⁴

What adverse effects have been associated with GLP-1 analogues?

Gastrointestinal adverse effects

The most frequent unwanted effects with exenatide are nausea (occurring in up to 57% of patients) and vomiting (in up to 17%).^{49,55} In trials, the incidence of nausea peaked during the first eight weeks of treatment and declined thereafter.⁵⁶⁻⁵⁸

As with exenatide, GI symptoms and anorexia are the commonest adverse effects reported with liraglutide^{54,59} and are most frequent during the first four weeks of treatment.⁶⁰⁻⁶² Nausea was reported by 10-56% of patients.^{60,62} Adverse GI events are most frequent with the combination of liraglutide and metformin; they are also more common among patients over 70 years and those with renal impairment.⁵⁴

Pancreatitis

Post-marketing reports of pancreatitis in exenatide-treated patients have emerged, with most patients having at least one risk factor for this condition.²⁶ If pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued.⁶³

Hypoglycaemia

Reports of episodes of severe hypoglycaemia with exenatide or liraglutide are rare. Mild to moderate hypoglycaemia have been reported when either exenatide or liraglutide are used in combination with a sulphonylurea.^{49,54,58} Episodes of mild hypoglycaemia are more common with exenatide than liraglutide (1.9 versus 2.6 per patient per treatment-year).⁶⁴

Have exenatide or liraglutide been shown to have an effect on body weight?

Therapy with exenatide is associated with significant and progressive weight loss that can manifest as early as week two,^{57,65,66} and is sustained for up to two years.⁶⁷ The reduction in body weight does not correlate with the occurrence of nausea,⁵⁶⁻⁵⁸ but appears to be directly proportional to patients' baseline BMI.⁶⁸ Liraglutide appears to have a similar effect on body weight.^{61,62,64}

Are there any clinically significant drug interactions with exenatide or liraglutide?

Exenatide

Because it slows gastric emptying, exenatide can decrease the rate and extent of absorption of other drugs. Oral drugs, particularly antibiotics and contraceptives, should be taken at

least one hour before injecting exenatide.^{53,69} Gastro-resistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after exenatide injection.⁵³ During post-marketing observation, increased INR has been reported during concomitant use of warfarin and exenatide. INR should be closely monitored during initiation and dose increase of exenatide therapy in patients on warfarin.⁵³

Liraglutide

Liraglutide has a very low potential for drug interactions.⁵⁴ The small delay in gastric emptying caused by liraglutide has not been shown to have any clinically relevant effect on the absorption of orally administered drugs.⁵⁴

Exenatide or liraglutide?

One disadvantage of exenatide, compared to liraglutide, is that it has to be administered twice a day. However, a long-acting version of exenatide (LAR) is in development with a possibility that it could be administered once a week.⁷⁰

Liraglutide is better at controlling blood glucose than exenatide; as shown by the findings of the LEAD-6 trial.⁶⁴ In adults with inadequately controlled type 2 diabetes who were taking metformin, sulphonylurea or both, liraglutide reduced HbA_{1c} by 1.12%, compared with 0.79% with exenatide.⁶⁴ In addition, 54% of patients on liraglutide achieved the blood sugar target of HbA_{1c} less than 7%, versus 43% of patients on exenatide.⁶⁴

What is the place of exenatide in the management of type 2 diabetes?

According to NICE, exenatide can be added to metformin and a sulphonylurea as a **third-line treatment option** for patients who satisfy the following criteria:

- BMI ≥ 35kg/m² and have specific psychological or medical problems associated with high body weight. Or,
- BMI < 35kg/m² but are not able to take insulin or have co-morbidities that would benefit from weight loss.

NICE states that exenatide should only be continued in patients who experience at least a 1% point reduction in HbA_{1c} and who lose at least 3% of their initial body weight after six months.

The NICE guideline does not mention liraglutide because it was not available at the time of publication. NICE is expected to publish a single technology appraisal for liraglutide in 2010. In the meantime, the institute's guidance for exenatide is likely to be applied to the use of liraglutide.

Table FIVE: Storage of exenatide and liraglutide^{53,54}

	Exenatide (Byetta® ▼)	Liraglutide (Victoza® ▼)
Storage prior to use	Store in a refrigerator (2°C to 8°C). Do not freeze.	
Storage in use	<ul style="list-style-type: none"> • Store below 25°C. • Do not store the pen with the needle attached. • Replace the cap on the pen to protect from light. • Use a pen for 30 days only. Dispose of pen after 30 days even if some drug remains in the pen. 	<ul style="list-style-type: none"> • Store below 30°C. • Do not store the pen with the needle attached. • Replace the cap on the pen to protect from light. • Use a pen for 1 month only. Dispose of pen after 1 month even if some drug remains in the pen.
Other	<ul style="list-style-type: none"> • Each pen is for use by one person only. • The instructions for using the pen must be followed carefully. • The injection should not be used if particles appear or if the solution is cloudy and/or coloured. • A pen that has been frozen must not be used. 	



CPD into action

► Consider carrying out audits of patients in your practice who have been on exenatide or liraglutide for at least six months:

- Has their HbA_{1c} come down by at least 1%?
- Have they achieved a weight loss of at least 3% of their initial body weight? If not, consider discontinuing the exenatide/liraglutide and/or seeking specialist advice.



Prescribing Note: Liraglutide ▼

- Liraglutide ▼ (Victoza® ▼) is supplied as a pre-filled pen containing 3mls of solution.
- Victoza® ▼ is available as a pack with 2 pens or a pack with 3 pens.
- Prescribers writing prescriptions for Victoza® ▼ should check the number of pens required. **Be careful to avoid prescribing 2 packs when 2 pens are intended.**
- Pharmacists should code for the number of pens dispensed. There are different codes for the 2-pen pack and the 3-pen pack.

Postprandial glucose regulators (repaglinide, nateglinide)

In the UK there are two postprandial glucose regulators, repaglinide (Prandin®) and nateglinide (Starlix®). These belong to a new class of agents which have been developed to specifically manage meal-related glucose fluctuations in patients with type 2 diabetes.

Mode of action

Postprandial glucose regulators increase the production and release of insulin by binding to a receptor site on the membrane of the pancreatic β-cell.⁷ Typically taken at the beginning of a meal, they induce an insulin surge, which fades rapidly, thus reducing the risk of later hypoglycaemia.⁷

Pharmacokinetics

Repaglinide is rapidly and almost completely absorbed after oral administration, with peak plasma concentrations achieved in about one hour.⁷¹ When taken about 15 minutes before a meal, repaglinide produces a prompt insulin-releasing effect, which is limited to about three hours, roughly coinciding with the duration of meal digestion.

Repaglinide is metabolised in the liver to inactive metabolites.⁷² The primary route of elimination of repaglinide and its metabolites is biliary-faecal excretion.⁷² The biliary excretion route indicates that repaglinide may be more suitable for use in patients with impaired kidney function than drugs which are eliminated by renal excretion (e.g. metformin).⁷²

When nateglinide is taken before meals, plasma levels of the drug peak within one hour, and plasma insulin concentrations rise rapidly, peak within two hours, and return to near baseline after four hours.⁷³ Nateglinide is metabolised in the liver, mainly by CYP2C9 and CYP3A4, and excreted in urine, with an elimination half-life of about 1.5 hours.

What are the most common side-effects of the postprandial glucose regulators?

Hypoglycaemia and weight gain are the most significant side-effects of postprandial glucose regulators.

Both repaglinide and nateglinide are capable of producing hypoglycaemia, although the overall incidence of hypoglycaemic episodes is lower with

Self-monitoring of blood

repaglinide or nateglinide than with sulphonylureas. Episodes of hypoglycaemia are mostly mild and easily handled through intake of carbohydrates. If severe, infusion of glucose may be necessary. The occurrence of such reactions depends, as for every diabetes therapy, on individual factors, such as dietary habits, dosage, exercise and stress. The risk of hypoglycaemia in patients receiving repaglinide or nateglinide appears to be increased when either of these agents is used in combination with metformin.^{74,75}

A small increase in bodyweight can be expected in patients starting repaglinide as initial monotherapy, but there may be little change in weight among patients switched from a sulphonylurea.⁷⁶ Nateglinide appears to have little effect on bodyweight when combined with metformin.⁷⁷

Other adverse effects associated with the postprandial glucose regulators include abdominal pain and diarrhoea.⁷⁸

Are repaglinide or nateglinide subject to any clinically significant drug interactions?

See **Table SIX**.

What are repaglinide and nateglinide licensed for?

Repaglinide is licensed for use in patients with type 2 diabetes:⁷⁸

- As **monotherapy** in people whose hyperglycaemia can no longer be controlled by diet and exercise alone, or
- As **dual oral therapy**, in combination with metformin, where metformin alone has not been satisfactory.

Nateglinide is licensed as **dual oral therapy**, in combination with metformin in type 2 diabetic patients inadequately controlled despite a maximally tolerated dose of metformin alone.⁷⁵

How should repaglinide or

nateglinide be taken?

Repaglinide should ideally be taken about 15-30 minutes before a meal.^{76,78} Starting with a low dose, e.g. 500 micrograms before each main meal, the effect on glycaemic control is monitored and the dosage titrated up every two weeks to a maximum of 4 milligrams before each main meal. The total maximum daily dose should not exceed 16 milligrams. If a meal is not consumed the corresponding dose of repaglinide should be omitted.

Nateglinide should be taken within 1-30 minutes before meals. The recommended starting dose is 60 milligrams three times daily before meals, particularly in patients who are near goal HbA_{1c}.⁷⁵ This may be increased to 120 milligrams three times daily.⁷⁵ Dose adjustments should be based on HbA_{1c} measurements. The recommended maximum single daily dose is 180 milligrams taken before the three main meals. Again, if a meal is missed, the dose should be omitted.

What results can be expected with postprandial glucose regulators?

Reductions in HbA_{1c} with repaglinide or nateglinide are similar in magnitude to those observed with sulphonylureas (i.e. 1-2%).^{76,77,79,80}

What is the place in therapy of the postprandial glucose regulators?

Repaglinide and nateglinide are relatively expensive drugs which are very similar to sulphonylureas in terms of their pharmacological action.⁵ However, the postprandial glucose regulators may have a role to play when younger patients have a lifestyle with variable eating patterns as the drugs can be taken immediately before a meal⁹ and in older patients where they may be at risk of hypoglycaemia with sulphonylureas.^{6,76}

Table SIX: Drug interactions with repaglinide or nateglinide^{75,78}

Drugs that may enhance and/or prolong the hypoglycaemic effect of repaglinide : Gemfibrozil, clarithromycin, itraconazole, ketoconazole, trimethoprim, ciclosporin, other antidiabetic agents, MAOIs, beta-blockers, ACE-inhibitors, salicylates, NSAIDs, octreotide, alcohol and anabolic steroids.	Drugs that may reduce the hypoglycaemic effect of repaglinide : Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.
The hypoglycaemic effect of nateglinide may be enhanced by ACE inhibitors.	The hypoglycaemic effect of nateglinide may be reduced by diuretics, corticosteroids, and β ₂ -agonists.

glucose in patients with type 2 diabetes.

Note: At the time of publication (July 2010) work is underway to develop regional guidance for Northern Ireland on self-monitoring of blood glucose in patients with type 2 diabetes (not on insulin).

In recent years spending on blood glucose test strips has increased dramatically. In 1999, spending in Northern Ireland on these agents was around £2million; by 2009 this had increased to £6million per year.

It is generally recognised that routine self-monitoring of blood glucose (SMBG) is beneficial, when supported with education, for all people with type 1 diabetes and those with type 2 diabetes using insulin. Such individuals can obtain a quick and accurate reading of their blood glucose level and use this information to adjust their insulin accordingly. In contrast, those with type 2 diabetes managed with hypoglycaemic agents typically *cannot* adjust their treatment in response to a specific blood glucose reading. The decision about whether or not SMBG is warranted in a person with type 2 diabetes should be made on a case-by-case basis, taking cognisance of the following points:

- SMBG is **unnecessary** in many patients, especially those who are either diet-controlled or taking only metformin and/or a gliatzone, to guard against hypoglycaemia. Glycaemic control should be adequately monitored using HbA_{1c} levels.
- SMBG has been shown to result in a modest reduction in HbA_{1c} of around 0.25%^{81,82} compared with no self-monitoring.
- Although statistically significant, it is unclear what this reduction in HbA_{1c} means clinically. There is a lack of evidence that SMBG improves quality of life, patient satisfaction, prevention of hypoglycaemia, long-term complications or leads to reduction in mortality.^{81,82}
- SMBG is not a stand-alone exercise and should only be introduced as an integral part of the patient's self-management plan. Patients and healthcare professionals should be clear what they hope to achieve. SMBG is only useful when the patient can use the results either to adjust management or to provide feedback.
- The possible advantages and disadvantages of SMBG should be explained to allow patients to make an informed choice on SMBG in the

management of their diabetes (See **Table SEVEN**).

- The usefulness and need for SMBG should be reviewed regularly and this should be clearly documented in the patient's notes.
- NICE recognises that, given the costs involved with SMBG, it should be "effectively deployed".

Are there particular patients with type 2 diabetes (who are not on insulin) who may benefit from SMBG?

NICE recommends that SMBG should be available to:⁹

- those on hypoglycaemic medications to provide information on hypoglycaemia (may be particularly pertinent for those on a sulphonylurea).
- assess changes in glucose control resulting from medications and lifestyle changes.
- monitor changes during intercurrent illness.
- ensure safety during activities, including driving.

If SMBG is considered to be necessary, how often should the patient measure their blood glucose level?

It is not possible to be specific about the ideal frequency of SMBG in type 2 diabetes. Therefore, an individual monitoring plan should be developed to include the frequency and timing of SMBG. This should be recorded in the patient's notes.

How should the usefulness or otherwise of SMBG be assessed?

The value of SMBG as an adjunct to therapy should be reviewed regularly. At a review, the key questions should be:⁹

- What action is prompted by the results of SMBG?
- If no action can be taken, what value does self-monitoring add to the patient's care?

Discussion should include the timing, frequency and results of testing, with advice dependant on overall control and stage of diabetes. The impact on quality of life should also be explored and any concerns about use of SMBG closely monitored. Since the accuracy of SMBG is instrument- and user-dependent, it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Remind patients that glucometers should be checked and re-calibrated at recommended intervals to ensure

accuracy.



CPD into action

- ▶ Identify patients with type 2 diabetes who are not on insulin and who are receiving SMBG strips on a regular basis.
- ▶ Carry out diabetic reviews where required.
- ▶ In consultation with patient, identifying cases where self-monitoring is considered **unnecessary**. Remove the strips from the patient's repeat medication record where required, and update the clinical notes accordingly.
- ▶ In consultation with patient, identifying cases where self-monitoring is considered **necessary**. Agree a monitoring plan according to the patient's particular needs and circumstances.
- ▶ Clearly document in the clinical notes including a timescale for review as necessary.

Websites:

- Association of British Clinical Diabetologists: www.diabetologists-abcd.org.uk
- NICE: www.nice.org.uk
- Diabetes UK: www.diabetes.org.uk

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Table SEVEN: Advantages and disadvantages of self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes (who are NOT on insulin)

Advantages of SMBG	Disadvantages of SMBG
Empowers patients	Lack of evidence that SMBG leads to better glycaemic control or clinical outcomes.
	Some people find testing painful. This can increase the psychological burden.
May maintain or improve motivation	Some people find testing demoralising, especially if results are outside the target range.
	Blood glucose monitoring strips are costly.

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COMPASS THERAPEUTIC NOTES ASSESSMENT Newer Drugs in Type 2 Diabetes

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.

Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. These can contribute 2-3 hours towards your CPD/CME requirements. Submit your completed MCQs to the appropriate address (shown below) or complete online at www.medicinesni.com. Assessment forms for each topic can be submitted in **any order** and at **any time**.

If you want extra copies of Therapeutic Notes and MCQ forms for this and any other topic you can: Visit the COMPASS Web site: www.centralservicesagency.n-i.nhs.uk/display/compass

or

Email your requests to: compass.team@hscni.net

or

Phone the COMPASS Team: 028 9053 5661

You can now complete your COMPASS multiple choice assessment questions and print off your completion certificate online:

- **Doctors and nurses should submit their answers at:** www.medicinesni.com
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Are you a

Pharmacist? Community Hospital Other (please specify) _____

GP? Enter your cipher number: _____

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Title: Mr/Mrs/Miss/Ms/Dr

Surname: _____ First name: _____

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GPs and Nurses:

Complete the form overleaf and return to:

COMPASS Unit

Family Practitioner Services

HSC Business Services Organisation

2 Franklin Street

Belfast

BT2 8DQ

Pharmacists:

Complete the form overleaf and return to:

Northern Ireland Centre for Pharmacy Learning & Development

FREEPOST NICPLD

Belfast BT9 7BL

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Successful completion of these assessment questions equates with **2 hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

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1 Regarding newer treatments for type 2 diabetes:

a	Exenatide was the first dipeptidylpeptidase-4 inhibitor to be licensed.	T	F
b	A significant number of patients using exenatide experience nausea.	T	F
c	Liraglutide is administered subcutaneously twice a day.	T	F
d	Dipeptidylpeptidase-4 inhibitors have a low risk of causing hypoglycaemia.	T	F

2 The following antidiabetic agents are weight neutral or can reduce a patient's weight:

a	Liraglutide	T	F
b	Saxagliptin	T	F
c	Rosiglitazone	T	F
d	Metformin	T	F

3 Thiazolidinediones:

a	NICE consider thiazolidinediones to be first-line agents in the management of type 2 diabetes.	T	F
b	After starting pioglitazone or rosiglitazone it may take up to 6-8 weeks before their full effect is achieved.	T	F
c	Dose adjustment is required in patients with hepatic impairment.	T	F
d	A reduction in HbA _{1c} of at least 0.5% over six months is considered to be an adequate response to a thiazolidinedione.	T	F

4 The administration of hypoglycaemic agents:

a	Repaglinide should be taken 15-30 minutes before a meal.	T	F
b	Gliptins can be administered with or without food.	T	F
c	Thiazolidinediones can be administered with or without food.	T	F
d	Nateglinide should be taken up to 30 minutes before a meal.	T	F

5 With regard to the self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes:

a	SMBG is a vital part of the management of all patients with type 2 diabetes.	T	F
b	There is robust evidence that SMBG in type 2 diabetes leads to better clinical outcomes.	T	F
c	SMBG may be useful for some patients on a sulphonylurea.	T	F
d	If a patient with type 2 diabetes (not on insulin) is using SMBG, they will need to use it long-term.	T	F