Newer therapies in type 2 diabetes: An introduction to the latest glucose-lowering agents

Jill Hill

Type 2 diabetes is a complex condition which, if not managed effectively, can lead to a range of expensive and debilitating microvascular and macrovascular complications. In the past few years, a number of new therapies for managing blood glucose have become available, making prescribing increasingly complex. This article aims to remind readers how blood glucose is regulated in the individual without diabetes, briefly discusses how older, "traditional" glucose-lowering agents work, and then describes the newest agents to become available. It is beyond the scope of the article to discuss all new therapies, so there is a focus on the latest arrivals in each class, specifically those that have been given a European licence in the previous 12 months (at time of writing). The description will include practical advice on who the agent is suitable for, the main side effects and concerns, as well as signposting to the key evidence.

The increasingly complex choice of agents available for blood glucose management reflects the increase in understanding of the complex regulation process that maintains normoglycaemia in people who do not have diabetes. The maintenance of blood glucose depends on a number of things:

- Sufficient endogenous insulin production.
- The sensitivity of muscle and adipose tissue to the effect of insulin.
- The processing of carbohydrate in the gut.
- The role of the liver (driven by the effect of glucagon produced by pancreatic alpha cells) in storing glucose as glycogen and manufacturing glucose through glycogenolysis (breakdown of glycogen) and gluconeogenesis (formation of glucose from other substrates).

The introduction of the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in recent years has raised awareness of the role of the incretin system in glucose homeostasis. After consumption of food, carbohydrate moves from the stomach into the small intestine and stimulates the production of incretin hormones in the gut. This stimulates appropriate beta cell insulin production, switches off inappropriate glucagon production (and therefore glucose production) and slows gastric emptying, thereby spacing out the glycaemic load.

The recent addition of a new class of therapies, the sodium glucose co-transporter 2 (SGLT2) agents, has raised awareness of the role of the kidney. As blood circulates through the renal system, the kidneys preserve glucose by the active re-absorption from glomerular filtrate, so it is not excreted in the urine.

Blood glucose management in people with type 2 diabetes

Type 2 diabetes is a condition of relative insulin deficiency (Reaven, 1988). For most people with the condition, central obesity reduces insulin sensitivity and the beta cells are unable to compensate for this resistance, resulting in

Citation: Hill J (2013) Newer therapies in type 2 diabetes: An introduction to the latest glucose-lowering agents. *Journal of Diabetes Nursing* **17**: 385–92

Article points

1. The increasingly complex choice of agents available for blood glucose management reflects the increase in understanding of the complex regulation process that maintains normoglycaemia.
2. The introduction of the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists focuses on the action of the incretin system and the recent addition of sodium glucose co-transporter 2 (SGLT2) agents has raised awareness of the role of the kidney.
3. This article focuses on the newest agents in four drug classes: DPP-4 inhibitors; GLP-1 receptor agonists; SGLT2 inhibitors and insulins. Only agents that have received a European licence in the previous 12 months will be discussed.

Key words

- Alogliptin
- Dapagliflozin
- Degludec
- Lixisenatide

Author

Author details can be found at the end of the article.

Table 1. Traditional glycaemic agents and their mode of action.

Agent	Main effect/site of action
Metformin	Reduces inappropriate hepatic glucose production
Sulphonylureas/ meglitinides	Stimulate beta cells to increase insulin secretion
Pioglitazone	Improves the insulin sensitivity of muscle and adipose tissue
Acarbose	Inhibits the enzyme alpha glucosidase that breaks down carbohydrate in the small intestine, thereby slowing postprandial glycaemic load
Insulin therapy	Supplements inadequate endogenous insulin

Table 2. New diabetes and their mode of action.

Agent	Main effect/site of action
DPP-4 inhibitors (gliptins)	Enhance the action of natural incretin hormone by inhibiting the enzyme that rapidly breaks down this hormone
GLP-1 receptor agonists	Mimic the action of natural incretin hormones and is more resistant to degradation by the DPP-4 enzyme
SGLT2 inhibitors	Inhibit the conservation of glucose by the kidneys, allowing excretion of glucose at blood glucose levels below the renal threshold
New insulins	Increasingly being developed to mimic the action of endogenous insulin and, particularly, to reduce the risk of hypoglycaemia, a significant barrier to achieving normoglycaemia.

hyperglycaemia. Lifestyle changes, such as increasing physical activity and losing weight, can improve insulin sensitivity and improve the effectiveness of endogenous insulin. As the condition progresses, oral medications are introduced to increase the production, or enhance the action, of insulin. However, for many people, supplementation with injected insulin is eventually required. *Table 1* summarises the older, "traditional" anti-diabetes agents that improve blood glucose regulation in type 2 diabetes.

Concerns about the unwanted effects of agents used in blood glucose management, such as hypoglycaemia and weight gain, as well as an increased awareness of the different processes involved in blood glucose regulation, has led to the development of newer therapies. *Table 2* summarises the main therapeutic action of these agents. It is beyond the scope of this article to discuss all agents in each drug class, so the focus will be on the agents that have been licensed in Europe in the previous 12 months (at time of writing).

DPP-4 inhibitors (gliptins)

Alogliptin

Alogliptin is the fifth DPP-4 inhibitor to be approved for use in Europe; it was approved in the European Union in September, 2013 (European Medicines Agency [EMA], 2013). The others are sitagliptin, vildagliptin, saxagliptin and linagliptin. Alogliptin will be available as 25 mg, 12.5 mg and 6.25 mg tablets, with the usual dose being 25 mg daily (EMA, 2013).

How does it work?

This class of agent inhibits DPP-4, which is an enzyme that degrades endogenous incretin hormones produced in the gut. Alogliptin, therefore, extends the action of GLP-1 in stimulating postprandial insulin production (Green et al, 2005). As production of GLP-1 is related to rising blood glucose levels, DPP-4 inhibitors are unlikely to cause hypoglycaemia or weight gain.

Who is it for?

Alogliptin is for people with type 2 diabetes over 18 years and can be used in combination with other glucose-lowering agents including insulin, when these combined with diet and exercise do not provide good glycaemic control (EMA, 2013).

As NICE type 2 guidelines are currently being revised, it is possible that alogliptin may not be included as it did not have its licence during the consultation period. It is likely, however, to be used in a similar way to the other DPP-4 inhibitors, which are currently recommended to be used in combination with metformin when a sulphonylurea is contraindicated or where the risk of hypoglycaemia is a concern (NICE, 2013a).

Are there any side effects or safety concerns?

No serious safety concerns have emerged so

far. Indeed, the EXAMINE (Examination of Cardiovascular Outcomes: Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) trial involving almost 5 400 people with diabetes has recently been published. This showed rates of major adverse cardiovascular events in people who had a recent acute coronary syndrome were not increased with alogliptin when compared with placebo (White et al, 2013).

The use of DPP-4 inhibitors has been associated with a potential risk of developing acute pancreatitis (EMA, 2013).

Is it effective?

Across the six randomised controlled trials (RCTs), the use of alogliptin (12.5 mg or 25 mg once daily) as an add-on therapy to a range of concurrent treatment options led to an additional reduction in HbA_{1c} of about 5.5 mmol/mol (0.5%), compared with placebo (NICE, 2013a). A summary of the evidence for alogliptin use is available from the NICE evidence summary: new medicine (ESNM)20 (NICE, 2013a).

GLP-1 receptor agonists

Lixisenatide

Lixisenatide is the fourth GLP-1 receptor agonist agent to become available; the others are exenatide, extended-release exenatide and liraglutide.

Lixisenatide is available in a single (green) 10 µg disposable pen device, a pack of two (purple) 20 µg disposable pen devices and as a starter pack of one 10 µg and one 20 µg pen (see dosing recommendations below).

How does it work?

Like the other GLP-1 receptor agonists, lixisenatide mimics the action of natural incretin hormone by interacting with GLP-1 receptors, stimulating insulin production from the pancreatic beta cells when blood glucose is increased but not when blood glucose is within the normal range. This helps avoid hypoglycaemia, if not compromised by other glucose-lowering agents that can cause hypoglycaemia. GLP-1 receptor agonists also suppress glucagon production, thereby reducing inappropriate hepatic glucose production. As it may slow gastric emptying and induce satiety, it can aid a reduction in calorie consumption and facilitate weight loss.

Who is it for?

Lixisenatide is for people with type 2 diabetes; it is licensed for use in combination with oral glucose-lowering agents (it has not yet been studied in combination with DPP-4 inhibitors) and/or basal insulin (electronic Medicines Consortium [eMC], 2013a).

Therapy commences with 10 µg injected subcutaneously once daily, within an hour before the first meal of the day or evening meal. This continues for 14 days after which the dose is changed to 20 µg once daily. If used in combination with sulphonylureas or insulin, a reduction in dose of the other therapies should be considered to reduce the risk of hypoglycaemia (eMC, 2013a).

It should not be used in people who are taking both insulin and sulphonylureas, due to the significantly increased risk of hypoglycaemia (eMC, 2013a). Severe renal impairment, type 1 diabetes and severe gastrointestinal disease are the other contraindications. Caution is recommended when using it in those with a history of pancreatitis. It has not been tested in women who are pregnant or breastfeeding and it is recommended that these women should discontinue lixisenatide (eMC, 2013a).

Are there any side effects or safety concerns?

The most common side effects are nausea, vomiting and diarrhoea (eMC, 2013a). Hypoglycaemia is a side effect when used in combination with insulin or sulphonylureas.

Acute pancreatitis has been associated with the use of GLP-1 receptor agonists, so individuals should be warned to stop using lixisenatide and seek urgent medical attention if they develop persistent severe abdominal pain (eMC, 2013a).

Is it effective?

A series of GetGoal trials looked at lixisenatide as monotherapy; with oral agents; with insulin; and compared with exenatide. Two trials

Page points

1. Lixisenatide is the fourth GLP-1 receptor agonist agent; the others are exenatide, extended-release exenatide and liraglutide.
2. Like the other GLP-1 receptor agonists, lixisenatide mimics the action of natural incretin hormone by interacting with GLP-1 receptors, stimulating insulin production from the pancreatic beta cells when blood glucose is increased but not when blood glucose is within the normal range.
3. Lixisenatide is for people with type 2 diabetes; it is licensed for use in combination with oral glucose-lowering agents (but not DPP-4 inhibitors) and/or basal insulin.

Page points

1. Dapagliflozin is the first in its category. It is available as 5 mg and 10 mg tablets. The usual dose is 10 mg daily, taken at any time. However, a 5 mg starting dose is recommended in people with severe hepatic impairment.
2. Dapagliflozin inhibits the action of a protein called sodium glucose co-transporter 2 (SGLT2), so less glucose is re-absorbed by the kidney, thereby promoting loss of glucose in the urine.
3. Dapagliflozin is indicated for people with type 2 diabetes, aged 18 and over as monotherapy where metformin is contraindicated, or with other oral agents and insulin.

found that lixisenatide was more effective than placebo with regard to reducing HbA_{1c} levels from baseline (up to 0.8–0.9% reduction; NICE, 2013b). An evidence summary of its effectiveness (ESNM26) is available from NICE (2013b). More details of lixisenatide, including trial results, can be found on the Summary of Product Characteristics (eMC, 2013a).

SGLT2 inhibitors

Dapagliflozin

Dapagliflozin is the first SGLT2 inhibitor to become available in the UK. It is available as 5 mg and 10 mg tablets (eMC, 2013b). The usual dose is 10 mg daily, taken at any time. However, a 5 mg starting dose is recommended in people with severe hepatic impairment (eMC, 2013b).

How does it work?

In an individual without diabetes, or in someone with diabetes with a blood glucose level that is below their renal threshold (usually less than 10 mmol/L), glucose does not appear in the urine; this is because a protein called sodium glucose co-transporter 2 (SGLT2) in the kidneys promotes the re-absorption of glucose from the glomerular filtrate in the initial part of the proximal tubules back into the bloodstream, so it is not excreted in the urine. SGLT2 inhibitors, such as dapagliflozin, inhibit the action of that protein so less glucose is re-absorbed by the kidney, thereby promoting loss of glucose in the urine. These agents can, therefore, aid weight loss through loss of calories in the urine, as well as lowering blood glucose level (eMC, 2013b).

Who is it for?

Dapagliflozin is indicated for people with type 2 diabetes, aged 18 and over as monotherapy where metformin is contraindicated, or with other oral agents and insulin (eMC, 2013b). However, no data are available for its combination with GLP-1 receptor agonists or DPP-4 inhibitors. Recent NICE approval recommends its use in combination with metformin as dual therapy, if used as described for DPP-4 inhibitors (NICE, 2009). NICE does not recommend it as a triple therapy with metformin and sulphonylurea (NICE, 2013c).

It is not recommended in combination with pioglitazone because, while a causal relationship between dapagliflozin and bladder cancer is unlikely, both agents appear to carry an increased risk of bladder cancer (Cummins, 2012; eMC, 2013b). Also, it should not be used in people using loop diuretics because it increases diuresis (eMC, 2013b). For the same reason, it should be stopped in circumstances where there is volume depletion (such as severe vomiting or diarrhoea). Its action depends on efficient renal function, so it is contraindicated in people with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2 (eMC, 2013b).

Are there any side effects or safety concerns?

The main side effect is increased hypoglycaemia, when used in combination with sulphonylureas or insulin. The doses of these should be reduced when starting dapagliflozin (eMC, 2013b). Urinary tract infections and particularly genital infections have been shown to be more common compared with placebo with or without other agents (NICE, 2013c).

When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (for example, blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin (eMC, 2013b). The numerical imbalance of breast, bladder and prostate tumours must be considered with caution and it will be further investigated in post-authorisation studies (eMC, 2013b).

Is it effective?

Five RCTs on dapagliflozin were submitted as evidence to NICE (three with metformin and two with insulin; NICE, 2013c). It would be useful to have study data directly comparing dapagliflozin with a DPP-4 inhibitor, given that both agents are alternative options to a sulphonylurea when considering intensifying metformin monotherapy; however, no data currently exist. Bailey et al (2010) looked at dapagliflozin added to metformin versus

metformin plus placebo. They found that at 24 weeks, there was a mean HbA_{1c} reduction of 0.84% with dapagliflozin 10 mg versus 0.30% with metformin and placebo. Trials also showed there was a statistically significant weight loss and reduction in blood pressure with dapagliflozin (NICE, 2013c). More details about dapagliflozin, including trial evidence, can be found on the Summary of Product Characteristics (eMC, 2013b)

New insulins

Degludec

Insulin degludec is a long-acting insulin analogue for basal insulin replacement therapy. It should be given once daily by subcutaneous injection only, at any time of day but preferably at the same time of day (eMC, 2013c).

It is available in two concentrations, 100 unit/mL available in a pre-filled pen device and in 3 mL cartridges for use with reusable devices, and 200 unit/mL available in a pre-filled pen device. The dosing system is designed so that the device for the 100 unit/mL pen dials up to 80 units (in 1 unit increments) and the pen for the 200 unit/mL strength dials up to 160 units (in 2 unit increments) even though the latter is double strength. As the dose counter of the device shows the number of units, irrespective of strength, no dose conversion is needed (Medicines and Healthcare Products Regulatory Agency [MHRA], 2013).

How does it work?

Degludec forms soluble multi-hexamers when injected subcutaneously, forming a depot from which the insulin is continuously and slowly absorbed. It lasts up to 42 hours, but should be given once daily (eMC, 2013c). A steady state should be achieved after 2 to 3 days of starting therapy. Although it is recommended to be given daily at the same time, there is no difference in effectiveness if it is given flexibly, so it may be helpful for people who struggle to have their basal insulin at a consistent time (for example, shift workers). However, there should be at least 8 hours between doses (eMC, 2013c).

When changing from another basal analogue insulin to degludec, there is no need to alter the dose but additional blood glucose monitoring is advised initially (MHRA, 2013).

Who is it for?

It can be used in people with type 1 (Heller et al, 2012) and type 2 diabetes (Garber et al, 2012) who require basal insulin. When considering type 2 diabetes, current NICE (2009) guidance recommends that, when insulin therapy is necessary, human neutral protamine hagedorn (NPH) insulin or isophane is the preferred option. Long-acting insulin analogues (glargine and detemir) can be considered as an alternative for some people who meet certain criteria, for example, those who require assistance from a healthcare professional. Although these insulins have a lower overall rate of hypoglycaemic episodes including nocturnal episodes, compared to NPH insulin, there is no significant difference in HbA_{1c} or severe hypoglycaemia rates but they are significantly more expensive (National Prescribing Centre, 2011). The use of NPH insulin instead of basal analogue insulins can result in considerable financial savings (Holden et al, 2011).

Degludec will be included in the next NICE type 2 diabetes management guidelines and the author assumes it will be reserved for people who meet certain criteria, similar to glargine and determir. Safety in children and young people under 18 years, and pregnant or breastfeeding women has not been established (eMC, 2013c).

Are there any side effects or safety concerns?

Like all insulin, hypoglycaemia is the main side-effect, albeit at a lower level of risk compared to other insulins (eMC, 2013c).

As discussed above, the pen devices used with this insulin have been designed so that the number of units is displayed on the dosing window; this means that, even if a person is given the incorrect strength, they will still get the correct dose. However, the MHRA has identified this as a source of concern. It advises that healthcare professionals should educate people to be aware of the different strengths and that people using degludec are given an "insulin passport" or "safety card" denoting the appropriate strength. Healthcare professionals should also ensure people

Page points

1. Degludec forms soluble multi-hexamers when injected subcutaneously, forming a depot from which the insulin is continuously and slowly absorbed. It can be used with both type 1 and type 2 diabetes.
2. As with all insulins, the main side effect of degludec is hypoglycaemia. Degludec has been shown to be non-inferior to insulin glargine.

"There was no difference in the rate of severe hypoglycaemia, although the findings relating to severe hypoglycaemia need to be viewed with caution because of very low event rates."

always dial up their dose by looking at the dose counter, not by listening to clicks (MHRA, 2013).

Is it effective?

Degludec has been shown to be non-inferior to insulin glargine and both basal insulins have been shown to reduce HbA_{1c} levels to a similar degree (NICE 2013d; NICE, 2013e). Although the absolute differences in rates were small, insulin degludec reduced the rate of overall hypoglycaemia (both daytime and nocturnal) compared with insulin glargine (NICE, 2013d). There was no difference in the rate of severe hypoglycaemia, although the findings relating to severe hypoglycaemia need to be viewed with caution because of very low event rates (NICE, 2013d). There are no published studies comparing insulin degludec with NPH (isophane) insulin, which is unfortunate, given the NICE recommendations described above. Evidence summaries for use in type 1 and type 2 diabetes (ESNM24; ESNM25) are available from NICE (2013d; 2013e). More details about degludec, including trial evidence, can be found on the Summary of Product Characteristics (eMC, 2013c).

New therapies and safety

All new therapies are designated "black

Table 3. The renal function restrictions of the newer diabetes therapies (adapted from the British National Formulary, 2013)

Medication and its usual recommended dose	Dose recommended in mild to moderate renal impairment	Dose recommended in severe renal impairment
Sitagliptin 100 mg daily	Reduce to 50 mg if eGFR is between 30 and 50 mL/min/1.73m^2	25 mg
Vildagliptin 50 mg twice daily (once daily in combination with sulphonylurea)	Reduce to 50 mg if eGFR is < 50 mL/min/1.73m^2	50 mg
Saxagliptin 5 mg daily	2.5 mg if eGFR shows moderate renal impairment	2.5 mg
Linagliptin 5 mg daily	No change in dose	No change in dose
Alogliptin* 25 mg daily	12.5 mg if eGFR between 30 and 60 mL/min/1.73m^2	6.25 mg
Exenatide 10 µg twice daily	Caution if eGFR between 30 and 50 mL/min/1.73m^2	Not recommended
Liraglutide 1.2 mg daily†	Not recommended if eGFR is < 60 mL/min/1.73m^2	Not recommended
Exenatide extended 2 mg weekly	Not recommended if eGFR < 50 mL/min/1.73m^2	Not recommended
Lixisenatide 20 µg	Caution if eGFR between 30 and 50 mL/min/1.73m^2	Not recommended
Dapagliflozin 10 mg	Not recommended if eGFR is < 60 mL/min/1.73m^2	Not recommended

* EMA (2013); † NICE (2010) recommended maximum dose

triangle" medications. Any apparent adverse events occurring in people taking these medications should be reported to the MHRA using the yellow card scheme (www.mhra.gov.uk/yellowcard).

Diabetes is associated with impaired renal function over time. As type 2 diabetes is progressive, choice and dosage of medication will be influenced by the degree of renal impairment. *Table 3* provides renal function restrictions for the newer therapies currently available, as adapted from the British National Formulary (2013), which gives eGFR units rather than creatinine clearance values often given in the Summaries of Product Characteristics.

Summary

Type 2 diabetes is progressive and management of blood glucose control becomes more challenging over time. There is now a comprehensive choice of medications available that enhance or inhibit the complex processes involved in glycaemic control. While they have advantages to offer in comparison with older therapies, in terms of acquisition cost, newer therapies are considerably more expensive than the older, "traditional" agents predominantly recommended by current NICE guidelines; furthermore, owing to their relatively recent availability, there will be less clinical experience to demonstrate their safety and effectiveness. When considering prescribing any medication, nurses will need to assess the individual and base their treatment decisions on whether the benefits outweigh the risks and disadvantages, as well as using local and national guidelines. ■

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"There is now a comprehensive choice of medications available that enhance or inhibit the complex processes involved in glycaemic control."

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. Which of the following statements is true?

A. Alogliptin is a new DDP-4 inhibitor: it has a single dose for all levels of renal impairment
B. Degludec is a new basal analogue insulin that can be given every 2 days instead of daily
C. Dapagliflozin increases the excretion of glucose in urine
D. Lixisenatide is not licensed for use with insulin

2. **Which two oral agents are not recommended in combination because they have been associated with an increased risk of bladder cancer?**

A. Dapagliflozin and glipizide
B. Pioglitazone and alogliptin
C. Dapagliflozin and pioglitazone
D. Lixisenatide and pioglitazone

3. Your patient has an eGFR of 38 mL/min/1.73m^2. Which of the following agents are licensed for use in an eGFR at this level?

A. Lixisenatide
B. Exanatide extended
C. Dapagliflozin
D. Liraglutide

4. Which of the following statements about degludec is true?

A. Reduce the dose when switching to degludec from another basal analogue insulin
B. There is a simple conversion process when changing someone from the 100 unit/mL to 200 unit/mL formulation
C. As degludec lasts for up to 42 hours, it only needs to injected every other day
D. Degludec reaches a steady state after 2 to 3 days

5. Which of the following statements about dapagliflozin is correct?

A. Dapagliflozin inhibits a protein in the kidney from selectively re-absorbing glucose from the glomerular filtrate
B. Dapagliflozin prevents glucose from being excreted in the urine
C. Dapagliflozin increases urine production to flush glucose from the blood circulating through the kidneys
D. Dapagliflozin promotes the action of a protein in the kidneys that selectively re-absorbs glucose from the glomerular filtrate

6. Which of the following statements about dapagliflozin is untrue?

A. Dapagliflozin should not be used in combination with pioglitazone
B. Dapagliflozin can be used in combination with insulin
C. A side effect of dapagliflozin is urinary tract and genital infections
D. Dapagliflozin should not be used with pioglitazone because both are associated with fluid retention

7. Which of the following statements about lixisenatide is untrue?

A. The starter packs for lixisenatide contain one 10 µg pen and one 20 µg pen
B. The device containing 10 µg is green and the device containing 20 µg is purple
C. The usual therapeutic dose for lixisenatide is 10 µg
D. Lixisenatide should be started at 10 µg daily and increased to 20 µg after 14 days

8. Which of the following statements is correct?

A. The dose of linagliptin should be reduced to 2.5 mg when eGFR is less than 50
B. The dose of vildagliptin is 50 mg daily when in combination with a sulphonylurea and 50 mg twice daily when in combination with metformin
C. Alogliptin 12.5 mg is recommended for patients with severe impairment
D. Sitagliptin 100 mg daily does not need to be reduced as eGFR falls

9. Which of the following statements is incorrect?

A. Dipeptidyl peptidase-4 degrades the endogenous incretin hormone GLP-1
B. Gliptins enhance the action of dipeptidyl peptidase-4
C. GLP-1 receptor agonists are resistant to degradation by dipeptidyl peptidase-4
D. Endogenous GLP-1 enhances postprandial insulin secretion

10. Which of the statements concerning safety is incorrect?

A. Lixisenatide should not be used in combination with sulphonylurea and insulin because of the risk of hypoglycaemia
B. Although the dose of degludec does not need reducing when changing from another basal analogue insulin, more frequent blood glucose monitoring is recommended initially
c. Dapagliflozin should be discontinued during episodes of severe vomiting
d. The dose of degludec should be reduced by 10% when changing from another basal analogue insulin