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Omarigliptin for the treatment of Type 2 diabetes mellitus

Abstract

Introduction:

The estimated global prevalence of diabetes mellitus for adults aged 20-70 in 2015 was 415 million with approximately 90% of diagnosed cases being Type 2 diabetes mellitus (T2DM). Improvements in lifestyle and effective therapies are key to management but due to the progressive nature of T2DM, pharmacotherapy is typically required. Whilst the initial therapy will usually be with metformin, thereafter treatment should be individualised, with consideration of several different second line options. These include the dipeptidyl peptidase-4 (DPP-4) inhibitors, of which omarigliptin is the second once weekly version.

Areas covered:

The paper summarises key pharmaco-dynamic and pharmacokinetic features and reviews the efficacy and safety trial data of omarigliptin, a once-weekly DPP-4 inhibitor.

Expert opinion:

Omarigliptin results in a significant improvement in glycaemia with an effective once weekly pharmacokinetic profile and low risk of drug-drug interactions. It has equivalent efficacy to existing once daily DPP-4 inhibitors and shares a similar side effect profile. It is weight neutral with a significantly lower risk of hypoglycaemia compared with sulphonylureas. Adherence to prescribed medication is poor in patients with T2DM. Once weekly omarigliptin is a welcomed addition to the therapeutic armoury but whether it will improve compliance remains to be seen.

Keywords:

Type 2 diabetes mellitus, Dipeptidyl Peptidase-4 (DPP-4) inhibitor, omarigliptin, compliance

1 Introduction

In 2006 the United Nations recognised diabetes as a global epidemic, the first non-infectious disease to be acknowledged as posing a worldwide health threat (1). The estimated global prevalence for adults aged 20-70 in 2015 was 415 million and this is expected to rise to 642 million by 2040 (2). Type 2 diabetes (T2DM) is responsible for approximately 90% of the diagnosed cases although a significant number of people with T2DM, approximately 1 in 2 (46%), remain undiagnosed (3). It is more common in deprived communities (75% of adults with T2DM live in low or middle income countries) and 5 million people die from diabetes-related illness each year (3). In the UK it's estimated to account for 10% of total NHS spend, largely due to the long-term complications caused by diabetes. Good glycaemic control reduces the risk of complications (4, 5, 6), particularly microvascular ones such as kidney disease and visual loss.

A healthy lifestyle is the cornerstone of T2DM management. Diet and exercise modifications are usually followed by or combined with pharmacological therapy. Metformin is the initial treatment of choice (7, 8) in the majority of individuals with T2DM. If the combination of metformin and healthy lifestyle fails to control glycaemia, additional glucose lowering medication is added. Traditionally the next step was a sulphonylurea due to its efficacy, low cost acquisition and availability. However as a result of glucose-lowering studies such as ACCORD (9) and ADVANCE (10), current guidelines (7, 8) recognise that treatment should be tailored to the individual. The result of this is that many different therapeutic options can and should be considered as possible 2nd line treatments. These include thiazolidinediones (7, 8), glucagon-like peptide-1 receptor agonists (GLP-1 RA) (8), sodium-glucose cotransporter 2 (SGLT2) inhibitors (7), DPP-4 inhibitors (7, 8) and insulin (8). Failure to achieve adequate control at this point would typically lead to triple therapy using combinations of the above medications.

T2DM occurs as a consequence of insulin resistance, and inadequate insulin secretion. Under normal circumstances nutrients in the small intestine and raised blood glucose levels lead to the release of incretin peptides, Glucagon-like peptide-1 (GLP-1) and Gastrointestinal peptide (GIP) into the circulation. These peptides cause a glucose-dependent release of insulin by activating G-protein coupled receptors on the surface of pancreatic β cells whilst GLP-1 also reduces hepatic glucose production by inhibiting glucagon secretion from islet α cells. The incretin peptides have a short plasma half life (1-2 minutes) as they undergo rapid enzymatic degradation by DPP-4. T2DM is associated with a significant reduction in GLP-1 production and intravenous infusion of GLP-1 restores normoglycaemia (11); hence elevation of endogenous GLP-1 levels by inhibiting its destruction was seen as a therapeutic target. Inhibition of DPP-4 using oral DPP-4 inhibitors, leads to an increased concentration of endogenous GLP-1 and GIP resulting in significant improvements in glycaemic control, and appears to have a greater efficacy in Asians than Caucasians (12). In addition, since insulin release induced by DPP-4 inhibitors is glucose-dependent, it is associated with significantly fewer episodes of hypoglycaemia than traditional therapy with sulphonylureas.

Eleven DPP-4 inhibitors have now been approved for use in man. There are seven once daily DPP-4 inhibitors: alogliptin, evogliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, and teneligliptin; two twice daily anagliptin and vildagliptin; and two once weekly trelagliptin and omarigliptin (13). Whilst these have different characteristics based on their unique chemical structures, clinical trials have failed to demonstrate a significant difference in efficacy. HbA1c reductions of 0.6-0.8% are typically recorded compared to placebo at the end of 12-24 week trials. Generally they are well tolerated, with low rates of hypoglycaemia unless added to insulin or insulin secretagogues (such as sulphonylureas), and are weight neutral, unlike sulphonylureas, insulin and thiazolidinediones which lead to weight gain.

2 Body of Review

2.1. Overview of the market

Type 2 diabetes is a chronic, lifelong condition which exposes sufferers to an increased risk of vascular complications. The complications can be divided broadly into macrovascular (cerebrovascular, cardiovascular and peripheral vascular disease) and microvascular (retinopathy, nephropathy and neuropathy). In addition to not smoking, key elements of management include control of blood pressure, lipids and glucose levels. As a result individuals with type 2 diabetes are often required to take multiple drug therapies in an attempt to control these risk factors but compliance has been shown to be poor (14). The development of once weekly products may simplify complex daily regimens and aid compliance.

Until March 2015 the only DPP-4 inhibitors available on the market were once or twice daily products. Since then two new once weekly gliptins have been approved in Japan (13), trelagliptin (March 2015) and omarigliptin (September 2015). Whether once weekly gliptin preparations will improve compliance and as a consequence glycaemic control remains to be seen but they are a welcome addition to the market.

2.2. Introduction to the compound

Omarigliptin is a once weekly dipetidyl peptidase-4 (DPP-4) inhibitor. Produced by Merck & Co. Inc., it received regulatory authority in Japan in September 2015 for monotherapy, or dual and triple therapy with other oral hypoglycaemics (15). It is generally prescribed at a dose of 25mg once weekly. There is no required dose reduction in mild or moderate renal impairment, but it needs to be reduced to 12.5mg once weekly in severe renal impairment (eGFR <30mls/minute/1.73m²). There are no dose restrictions with any degree of hepatic impairment (16).

2.3. Chemistry

The molecular formula of omarigliptin (MK-1032) is $C_{17}H_{20}F_2N_4O_3S$, (Box 1), with a molecular weight of 394.4 g/mol.

Omarigliptin is created by a reductive amination of tetrahydropyranone with methylsulfonylpyrrolopyrazole in the presence of triacetoxyborohydride in dimethylacetal. The intermediates produced by this are then subject to deprotection and neutralisation with ammonium hydroxide, and crystallisation from ethyl acetate to form omarigliptin (17).

2.4. Pharmacodynamics

Omarigliptin exhibits dose-dependent DPP-4 inhibition (17). Trough DPP-4 activity is inhibited by approximately 90%, leading to a 2-fold postprandial increase in mean active GLP-1 and a significant postprandial glucose reduction compared with placebo (18). In line with other DPP-4 inhibitors it is well tolerated, weight neutral and has a low incidence of symptomatic hypoglycaemia (19).

2.5. Pharmacokinetics and metabolism

Omarigliptin is a reversible competitive inhibitor of DPP-4, which is more potent than sitagliptin the current market leader (IC_{50} omarigliptin 1.6nM, sitagliptin 18nM) (17). The pharmacokinetic profile of omarigliptin is biphasic with a long terminal half-life of >100 hours which allows for a once weekly dosing regimen. It is rapidly absorbed, the AUC and C_{max} of omarigliptin is proportional to the dose used, reaching a steady state within 2-3 weeks. (17, 18). There is minimal accumulation after multiple dosing, which suggests that omarigliptin reaches therapeutic levels with the first dose (18).

The pharmacokinetic profile of omarigliptin has been shown to be the same in obese individuals with and without T2DM (18). It does not require restrictions based on an individual's demographics nor the timing of meals since food, age, gender, obesity and race do not appear to have a significant effect on its pharmacokinetic profile.

Omarigliptin is eliminated largely unchanged in the urine (74.4%) having undergone minimal metabolism. A small amount (3.4%) has also been recovered from faeces. Whilst several minor metabolites have been found in the urine no active metabolites have been identified to date. Its excretion does not appear to be meaningfully altered by mild or moderate renal impairment and as a result no dose adjustment is required. Individuals with significant renal impairment, and end stage renal disease requiring haemodialysis however, experience a 1.6 and 2 fold increase in AUC respectively (20). A 50% dose reduction (omargliptin 12.5mg once weekly) is recommended in this situation.

2.6 Clinical efficacy

2.6.1. Glycaemia

Phase I

Administration of omarigliptin in single and multiple doses in two phase I double blind, randomised, placebo controlled studies of healthy volunteers led to a 2 fold rise in mean active GLP-1 concentrations in keeping with its mechanism of action as a DPP-4 inhibitor (21). A similar increase in mean active GLP-1 was seen in response to 50mg omarigliptin in obese individuals with and without diabetes, as well as a significant reduction in post-meal glucose of 0.7 mmol/L compared to placebo (18). Omarigliptin was associated with a non-significant reduction in weight which is consistent with the weight neutral effect of other DPP-4 inhibitors (22).

Phase II

In a 12 week phase II, double-blind, randomised, dose ranging study assessing the effect of omarigliptin 0.25mg, 1mg, 3mg, 10mg or 25mg once weekly against placebo in individuals with T2DM the greatest improvement in glycaemic control was seen with the 25mg dose of omarigliptin (19). There was a significant ($p < 0.001$) improvement in HbA1c -0.72% ($-0.93, -0.5$), 2 hour post meal glucose -2.5 mmol/L ($-3.3, -1.7$), and fasting plasma glucose -1.3 mmol/L at 12 weeks. Similarly a greater proportion of individuals on omarigliptin 25mg once weekly achieved the HbA1c target $<7.0\%$ (33.6% v 21.8%), or $<6.5\%$ (13.6% v 4.5%) compared with placebo.

Subjects completing the baseline study (18) were eligible to join a 66 week extension study (Table 1). All individuals in the omarigliptin arm, including those initially on 25mg, were given omarigliptin 25mg once weekly whilst the placebo arm were initially treated with blinded pioglitazone and later metformin. At the end of the 66 week extension the percentage of individuals achieving an HbA1c target of $<7.0\%$ and $<6.5\%$ increased with increasing omarigliptin dose, but there was no significant difference in HbA1c target attainment between the placebo/metformin arm (45.8% & 29.2% respectively) and those who had initially been given and continued to receive omarigliptin 25 mg in the extension study (43.5% & 21.7% respectively). There was a gradual deterioration in glycaemic control for all treatment groups towards the end of the extension study, which appeared similar to that observed with other glucose lowering treatments (5, 6). Weight neutrality was observed in both the baseline and extension study.

Phase III

The clinical development programme for omarigliptin O-QWEST (Omarigliptin Q Weekly Efficacy and Safety in Type 2 Diabetes) involves 10 Phase III clinical trial and approximately 8000 patients with T2DM.

In a 24 week, phase III, head to head study in subjects with T2DM (Table 1) inadequately controlled on metformin, omarigliptin 25mg once weekly achieved its primary endpoint and was non-inferior to sitagliptin 100mg once daily at reducing HbA1C levels from baseline (omarigliptin -0.47%; sitagliptin -0.43% (difference -0.03% [95% CI -0.15 to 0.08])). In addition, a similar number of patients achieved an HbA1C <6.5% (omarigliptin 27%; sitagliptin 23% (p=0.212)) (23).

A 54 week, head-to-head, phase III trial in people with T2DM (Table 1) inadequately controlled with metformin comparing add on therapy with omarigliptin 25mg once weekly to glimepiride titrated as required up to a maximum of 6mg once daily, failed to demonstrate any significant difference in HbA1c (omarigliptin -0.30% (-0.39 to -0.21) v glimepiride -0.48% (-0.57 to -0.39)) or fasting plasma glucose (omarigliptin -0.15mmol/L (-0.37 to 0.07) v glimepiride -0.46 mmol/L (-0.69 to -0.24)) between the two arms. Numerically, fewer subjects attained an HbA1c target <7.0% (omarigliptin 47.7% (42.3 to 53.1) v glimepiride 58% (52.7 to 63.1)) or <6.5% (omarigliptin 25.1% (20.6 to 30.2) v glimepiride 28.8% (24.1 to 34.0)) on omarigliptin than with glimepiride. There was, however, a significant increase in the number of participants experiencing symptomatic hypoglycaemia with glimepiride compared with omarigliptin (26.7% v 5.3% (p<0.001)) and in weight compared to baseline (1.5kg (1.1 to 1.9) v -0.4 Kg (-0.8 to 0.0) (p<0.001)) (24).

In a recently completed phase III, multicenter, randomized, double-blind, placebo-controlled trial (Table 1) the addition of omarigliptin 25mg once weekly to individuals with T2DM inadequately controlled on a combination of metformin and glimepiride (triple therapy) significantly reduced

HbA1c by -0.67% (-0.84 to -0.50) compared with placebo -0.06% (-0.23 to 0.12) ($p < 0.001$) (25).

The omarigliptin arm also achieved its secondary endpoint targets of a significant reduction in fasting plasma glucose compared to placebo (-1.1 v -0.2 mmol/L ($p < 0.001$)) and a significantly higher percentage attained HbA1c target of $< 7.0\%$ (23.8% v 4.4% ($p < 0.001$)) and $< 6.5\%$ (10.1% v 2.1% ($p < 0.01$)).

2.6.2. Ongoing trials of interest:

Phase III trials designed to assess the safety and efficacy of omarigliptin in young adults (26), and those with increasingly severe renal impairment including established haemodialysis (27) have recently completed and results are awaited.

2.7. Safety and Tolerability

The adverse events in phase I and II studies have tended to be mild and transient. The most frequently reported adverse events attributed to omarigliptin were headaches, dizziness, and nausea (17, 28). There have been no consistent abnormalities in the history, physical examination, laboratory safety tests (lipids (TC, HDL, LDL & Tg), liver function, creatinine kinase, creatinine and eGFR) or ECG studies, including a detailed QTc study (29).

Omarigliptin is largely renally excreted. Phase I studies have identified the need to reduce the dose from 25mg to 12.5mg once weekly in presence of severe renal impairment (eGFR $< 30\text{mls/minute}/1.73\text{m}^2$) or end stage renal disease but no adjustment is required with hepatic impairment (16).

Adverse event data in Phase III trials appears to be consistent with safety data from Phase I and II trials. In a recent phase III study comparing omarigliptin 25mg once weekly against sitagliptin

100mg OD a similar number experienced serious (omarigliptin 11 (3.4%) verses sitagliptin 9 (2.8%)) or drug related (omarigliptin 123 (3.7%) verses sitagliptin 12 (3.8%)) adverse events, and there was no significant difference in the number who discontinued (omarigliptin 3 (0.9%) verses sitagliptin 7 (2.2%)) 95% CI -3.6 to 0.8 in both study arms. Symptomatic and asymptomatic hypoglycaemia was recorded in 3.7% of the omarigliptin group (one severe) compared with 4.7% of the sitagliptin group, whilst the commonest recorded adverse events were diarrhoea, influenza, urinary tract infection, lipase increase and back pain (Table 2).

A randomized, double-blind, placebo-controlled study assessing cardiovascular outcomes following treatment with omarigliptin in 4000 subjects with T2DM has recently been terminated by Merck as it no longer plans to submit a marketing application in the United States or Europe (30). There were no additional efficacy or safety concerns reported during this study.

2.7.1. Interactions:

Omarigliptin does not inhibit cytochrome p450s (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), phase 2 enzymes (UGT1A1, SULT1E1) or key drug transporters (human P-gp, BCRP, OATP1B1, OATP1B3, hOAT1, hOAT3, hOCT1, hOCT2) nor does it induce CYP1A2, CYP2B6 or CYP3A4. It therefore has low risk of drug-drug interactions.

2.7.2. Post-marketing surveillance

Omarigliptin was launched in Japan during the last quarter of 2015. To date post marketing surveillance studies have not been published.

In summary the incidence of hypoglycaemia is low and comparable to placebo. There are currently no significant concerns identified to suggest that omarigliptin has a different safety profile to daily dosed DPP-4 inhibitors.

2.8. Regulatory affairs

Omarigliptin received regulatory authority in Japan in September 2015 for monotherapy, or dual and triple therapy with other oral hypoglycaemics (15). Currently there are no plans to submit additional marketing applications.

3 Conclusion

Omarigliptin is a once weekly DPP-4 inhibitor with equivalent efficacy to once daily preparations. The therapeutic effect of DPP-4 inhibitors relates to their effectiveness in inhibiting DPP-4 enzyme rather than a direct end-organ effect. Since the DPP-4 inhibitors generally have a similar effect on the enzyme they have equivalent efficacy.

The incidence of hypoglycaemia is low and comparable to placebo but in keeping with all DPP-4 inhibitors will be increased when combined with sulphonylureas or insulin. To date, no significant concerns have been identified to suggest that omarigliptin has a different safety profile to daily dosed DPP-4 inhibitors. It appears to have a low risk of drug-drug interactions.

Omarigliptin has a licence for mono, dual or triple therapy and is prescribed at a dose of 25mg once weekly. There is no required dose reduction in mild or moderate renal impairment, but it needs to be reduced to 12.5mg once weekly in severe renal impairment (eGFR <30mls/minute/1.73m²).

There are no dose restrictions with any degree of hepatic impairment (16).

4 Expert opinion

Whilst diet and lifestyle remain the cornerstone of T2DM management there is a need to develop safe, efficacious treatments which improve compliance. Omarigliptin is the second once weekly

DPP-4 inhibitor to be licenced. It results in a significant improvement in glycaemia with an effective once weekly pharmacokinetic profile. It has equivalent efficacy to existing once daily DPP-4 inhibitors, and shares a similar side effect profile. Omarigliptin is weight neutral with a significantly lower risk of hypoglycaemia than sulphonylureas. Deterioration in glycaemic control was seen at the end of an 18 month extension study, as seen with other glucose lowering treatments which do not appear to impact on the progressive nature of hyperglycaemia in T2DM.

The decision not to licence omarigliptin in the European Union and United States was not made because of safety concerns and appears to have been based on marketing considerations. This contrasts markedly with the development of GLP-1RAs, where three once weekly preparations are currently licenced in western countries and more are being assessed in phase 3 trials. These differences probably reflect the therapy algorithms prevalent in different regions and the mode of administration of these different incretin classes, as outlined below.

The ADA/EASD position statement (31) for the management of T2DM recommends metformin as first-line therapy in all cases (except those for whom it is contraindicated). Metformin, an oral preparation, is given on a daily basis often in divided doses so as to improve tolerability. Even the extended release versions of metformin are often administered twice daily to reduce side-effects.

ADA/EASD (31) recommends DPP-4 inhibitors as a possible second-line after metformin and so the convenience of omarigliptin being a once weekly administration is negated by being on a background of multiple daily dosing. Moreover, it is possible that compliance with the currently available once daily DPP-4 inhibitors might be better than with a once-weekly version in this setting. In the UK and some other countries, economic considerations lead to DPP-4 inhibitors being used as third-line agents (after metformin and sulphonylureas or pioglitazone). This further dilutes the potential advantage of once weekly omarigliptin.

The ADA/EASD position statement (31) also recommends that GLP1-RAs are considered as a second-line therapy after metformin although other guidelines (e.g. from the National Institute for Health and Care Excellence (32)) position them after failure of triple oral therapy. In any event, they are all currently injectable agents and so many patients will prefer less frequent administration. In addition, there is emerging evidence that long-acting GLP1-RA therapy may have cardiovascular advantages over shorter acting agents.

In Japan, metformin has never achieved the primacy over other anti-diabetes therapies seen in the West. Sulphonylureas have headed traditional guidelines and here the DPP-4 inhibitors have made major in-roads into the diabetes therapies marketplace. This is due to their advantages of low hypoglycaemia and weight neutrality over the sulphonylureas. So, for many clinicians, DPP-4s are the first line therapy for T2DM and the option of once weekly omarigliptin versus daily therapies is more obvious. It may also represent a more ‘gradual’ introduction of treatment which may be attractive for patients. Whether once weekly omarigliptin will improve compliance and, thereby, produce better levels of glycaemic control in real-world conditions remains to be seen.

Future research and development in the DPP-4 field is likely to be influenced by results from cardiovascular outcome trials (CVOTs) in other classes of anti-diabetes agents. There have now been three CVOTs of DPP-4 inhibitors (saxagliptin (33), alogliptin (34) and sitagliptin (35)) which confirmed their primary end-point – demonstration of non-inferiority for a composite cardiovascular (CV) endpoint versus placebo. However, CVOTs of empagliflozin (36) (an oral SGLT2 inhibitor), liraglutide (37) and semaglutide (38) (once daily and once weekly GLP-1RAs respectively) not only showed non-inferiority but were also found to be superior with respect to their CV endpoint. If these results are confirmed as class effects, generalisable to T2DM patients at lower levels of CV risk than those included in the current trials, then it is likely that DPP-4

inhibitors will move down the treatment algorithms. This will especially be the case if the on-going development of an oral GLP-1RA (semaglutide) is successful. In this scenario, further development of the largely off-patent DPP-4 class may be limited.

TABLES

Table 1 Efficacy of Omarigliptin in individuals with Type 2 diabetes mellitus

Phase and Type of trial, Comparator treatment arms		HbA1c (%)	FPG (mmol/L)	Achieved HbA1c <7%	Achieved HbA1c <6.5%
Phase II Mono	Omarigliptin 25mg qw	-0.57 (-0.73 to -0.42)	-1 (-1.3 to -0.7)	33.6%	13.6%
	Placebo	0.14 (0.01 to 0.3)	0.3 (0.0 to 0.6)	21.8%	4.5%
	Significance	(p<0.001)	(p<0.001)	(NS)	(NS)
Phase III Dual	Omarigliptin 25mg qw	-0.47	-0.8	54.4%	28.8%
	Sitagliptin 100mg OD	-0.43	-0.5	52.4%	24.4%
	Significance	(NS)	(NS)	(NS)	(NS)
Phase III Dual	Omarigliptin 25mg qw	-0.3 (-0.39 to -0.21)	-0.15 (-0.37 to -0.07)	47.7%	25.1%
	Glimepiride 1-6mg OD	-0.48 (-0.57 to -0.39)	-0.46 (-0.69 to -0.24)	58.0%	28.8%
	Significance	(NS)	(NS)		(NS)
Phase III Triple	Omarigliptin 25mg qw	-0.67 (-0.84 to -0.5)	-1.1	23.8%	10.1%
	Placebo	-0.06% (-0.23 to 0.12)	-0.2	4.4%	2.1%
	Significance	p<0.001	p<0.001	p<0.001	p<0.001

Dual therapy = Metformin (≥1500mg) plus Omarigliptin versus Sitagliptin or Glimepiride
 Triple therapy = Metformin (≥1500mg), and Glimepiride (≥4mg) plus Omarigliptin or placebo.
 (NS) = Not significant

Table 2 Adverse events with incidence ≥2% in one or more treatments in patients with Type 2 diabetes mellitus in a phase III trial comparing Omarigliptin with Sitagliptin

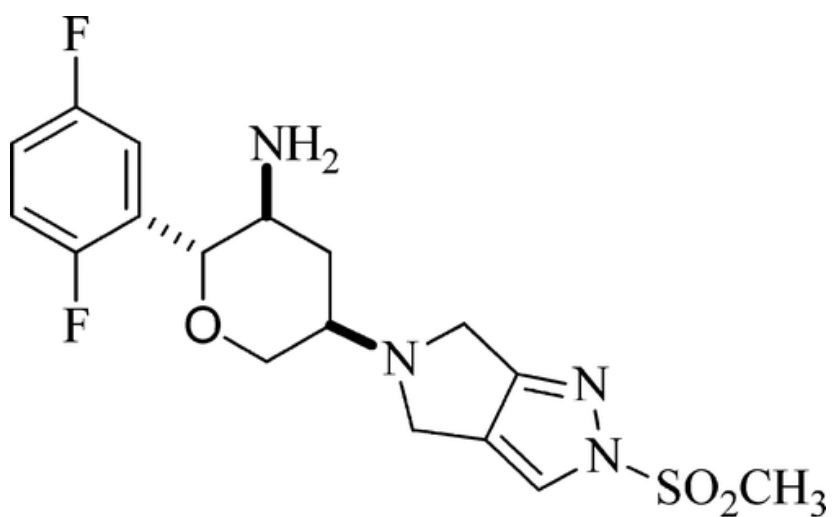
	Omarigliptin	Sitagliptin
Diarrhoea	0.9%	2.8%
Influenza	0.3%	2.2%
Urinary tract infection	1.2%	2.8%
Lipase increase	2.5%	4.1%
Back pain	2.5%	0.6%
Any hypoglycaemia (symptomatic or asymptomatic)	3.7%	4.7%
Severe hypoglycaemia	1 event	No events

BOX

BOX 1 Drug Summary

Drug name	Omarigliptin
Indication	Type 2 diabetes mellitus
Route of administration	Oral
Mechanism of action	blockade of dipeptidyl peptidase-4 (DPP-4)

Chemical structure



(Adapted from Biftu T et al. A novel long-acting DPP-4 inhibitor for once-weekly treatment of Type 2 diabetes. *Journal of Medicinal Chemistry* 2014;57:3205-3212)

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