ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets
Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets

Each tablet contains 850 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets

Each tablet contains 1,000 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Excipient with known effect

Each tablet contains 48 mg of lactose (as anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablet (tablet).

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets

Beige, biconvex, 11 x 21 mm oval tablet, with 3005 debossed on one side.

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets

Green, biconvex, 11 x 21 mm oval tablet, with 3002 debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Qtrilmet is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control.
- when already being treated with metformin and saxagliptin and dapagliflozin.

4.2 Posology and method of administration

Posology

Each tablet contains a fixed dose of metformin, saxagliptin and dapagliflozin (see section 2). If no adequate strength of Qtrilmet is available, individual mono-components should be used instead of the modified-release combination.

The maximum recommended daily dose of Qtrilmet is metformin 2,000 mg/saxagliptin 5 mg/dapagliflozin 10 mg.

For patients inadequately controlled on dual combination with either saxagliptin or dapagliflozin and metformin
Patients should receive a total daily dose of Qtrilmet equivalent to saxagliptin 5 mg, dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. The dose should be taken as two tablets orally, once daily at the same time of the day, with food.

Switching from separate tablets of metformin, saxagliptin and dapagliflozin
Patients switching from separate tablets of metformin, saxagliptin 5 mg and dapagliflozin 10 mg to Qtrilmet should receive the same daily dose of metformin, saxagliptin and dapagliflozin already being taken or the nearest therapeutically appropriate dose of metformin. The dose should be taken as two tablets orally, once daily at the same time of the day, with food.

Switching from metformin immediate-release to metformin modified-release
In patients switching from metformin immediate-release to metformin modified-release, the dose of Qtrilmet should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose (see sections 5.1 and 5.2).

Missed doses
If a daily dose is missed and it is ≥ 12 hours until the next dose, the dose should be taken. If a daily dose is missed and it is < 12 hours until the next dose, the missed dose should be skipped and the next dose taken at the usual time.

<u>*Special populations*</u>

Elderly
Because elderly patients (≥ 65 years) are more likely to have decreased renal function, this medicinal product should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin associated lactic acidosis, particularly in elderly patients (see sections 4.3 and 4.4). Risk of volume depletion with this medicinal product should also be taken into account (see sections 4.4 and 5.2). Due to the limited therapeutic experience with this medicinal product in patients 75 years and older, initiation of therapy is not recommended in this population.

Renal impairment
No dose adjustment is recommended for Qtrilmet in patients with mild renal impairment, GFR 60-89 mL/min.

A GFR should be assessed before initiation of treatment with metformin containing medicinal products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

This medicinal product should not be used in patients with moderate to severe renal impairment (patients with GFR < 60 mL/min (see sections 4.4, 4.8, 5.1 and 5.2). This medicinal product is contraindicated in patients with GFR < 30 mL/min (see sections 4.3, 4.4, 4.8 and 5.2).

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment (see section 4.3).

Paediatric population
The safety and efficacy of this medicinal product in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

<u>Method of administration</u>

Qtrilmet dose is taken orally once daily at the same time of the day with food to reduce the gastrointestinal adverse reactions associated with metformin. Each tablet is to be swallowed whole.

Occasionally, the inactive ingredients of this medicine will be eliminated in the faeces as a soft, hydrated mass that may resemble the original tablet.

4.3 Contraindications

Qtrilmet is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients listed in section 6.1, history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase-4 (DPP-4) inhibitor or to any sodium-glucose co-transporter 2 (SGLT2) inhibitor (see sections 4.4, 4.8 and 6.1);
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (see sections 4.4 and 4.8);
- diabetic pre-coma (see section 4.4);
- severe renal failure (GFR < 30 mL/min) (see sections 4.2, 4.4 and 5.2);
- acute conditions with the potential to alter renal function such as:
    - dehydration,
    - severe infection,
    - shock;
- acute or chronic disease which may cause tissue hypoxia such as:
    - cardiac or respiratory failure,
    - recent myocardial infarction,
    - shock;
- hepatic impairment (see sections 4.2 and 5.2);
- acute alcohol intoxication, alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Qtrilmet should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as anti-hypertensives, diuretics, and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting, and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia, and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Qtrilmet and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/litres. It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms, such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with Qtrilmet should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with Qtrilmet may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating Qtrilmet, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery, or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy in patients with type 1 diabetes have not been established and Qtrilmet should not be used in patients with type 1 diabetes. In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency.

Monitoring of renal function

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate to severe renal impairment (patients with GFR < 60 mL/min), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH), and hypotension, compared with placebo. Therefore, Qtrilmet should not be used in patients with moderate to severe renal impairment (patients with GFR < 60 mL/min). This medicinal product has not been studied in severe renal impairment (GFR < 30 mL/min) or end-stage renal disease (ESRD).

Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis (see section 4.4).

Renal function should be assessed:
- prior to initiation of this medicinal product and regularly thereafter (see sections 4.2, 4.8, 5.1 and 5.2);
- prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter (see section 4.5);

- for renal function with GFR levels approaching moderate renal impairment and in elderly patients, at least 2 to 4 times per year. If renal function falls below GFR < 60 mL/min, treatment should be discontinued.

Metformin is contraindicated in patients with GFR of < 30 mL/min and this treatment should be temporarily interrupted in the presence of conditions that alter renal function (see section 4.3).

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a NSAID.

Use in patients at risk for volume depletion, hypotension, and/or electrolyte imbalances

Due to dapagliflozin's mechanism of action, Qtrilmet increases diuresis associated with a modest decrease in blood pressure (see section 5.1), which may be more pronounced in patients with very high blood glucose concentrations.

This medicinal product is not recommended for use in patients at risk of volume depletion (e.g. receiving loop diuretics) (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as acute gastrointestinal illness with nausea, vomiting or diarrhoea).

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

For patients receiving Qtrilmet, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests, including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, this medicinal product should be discontinued; if acute pancreatitis is confirmed, it should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In post-marketing experience of saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Qtrilmet should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Hypersensitivity reactions

During post-marketing experience with saxagliptin, including spontaneous reports and clinical trials, the following adverse reactions have been reported with the use of saxagliptin: serious hypersensitivity reactions, including anaphylactic reaction, anaphylactic shock, and angioedema. Qtrilmet should be discontinued if a serious hypersensitivity reaction is suspected. The event should be assessed and alternative treatment for diabetes should be instituted (see section 4.8).

Urinary tract infections

Treatment with SGLT2 inhibitors increases the risk for urinary tract infections (see section 4.8). Patients with signs and symptoms of urinary tract infections should be evaluated and promptly treated, if indicated.

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving dapagliflozin and other SGLT2 inhibitors. Temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.

Elderly

Elderly patients are more likely to have impaired renal function, and may be at a greater risk for volume depletion. In addition, elderly patients are more likely to be treated with anti-hypertensive medicinal products that may cause volume depletion and/or changes in renal function [e.g. angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB)]. Therefore, renal function and risk of volume depletion should be taken into account prior to starting treatment with Qtrilmet. The same recommendations for monitoring of renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared with placebo (see section 4.8).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies with saxagliptin (see section 5.3). Skin lesions were not observed at an increased incidence in saxagliptin clinical trials. Post-marketing reports of rash have been described in the DPP-4 inhibitor class. Rash is also noted as an adverse reaction for this medicinal product (see section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration, or rash, is recommended.

Bullous pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including saxagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving saxagliptin and bullous pemphigoid is suspected, this medicinal product should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8).

Cardiac failure

Experience in NYHA class I-II is limited in dapagliflozin. There is no experience in clinical trials with dapagliflozin in NYHA class III-IV. Experience in NYHA class III-IV is limited with saxagliptin.

In the SAVOR trial, a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin-treated patients compared to placebo, although a causal relationship has not been established (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes.

Caution is warranted if Qtrilmet is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia

Joint pain, which may be severe, has been reported in post-marketing reports for DPP-4 inhibitors (see section 4.8). Patients experienced relief of symptoms after discontinuation of the medicinal product and some experienced recurrence of symptoms with reintroduction of the same or another DPP-4 inhibitor. Onset of symptoms following initiation of therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of therapy should be individually assessed.

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome have not been studied in the saxagliptin clinical programme. The efficacy and safety profiles of Qtrilmet in these patients have not been established.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Use with insulin or insulin secretagogues known to cause hypoglycaemia

Both saxagliptin and dapagliflozin can individually increase the risk of hypoglycaemia when combined with insulin or an insulin secretagogue (sulphonylurea). Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur during concomitant use with other glucose-lowering agents. Therefore, a lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycaemia when these agents are used in combination with Qtrilmet (see sections 4.5 and 4.8).

Surgery

Qtrilmet must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Qtrilmet should be discontinued prior to, or at the time of, the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Elevated haematocrit

Haematocrit increase was observed with dapagliflozin treatment, (see section 4.8); therefore, caution in patients with already elevated haematocrit is warranted.

Urine laboratory assessments

Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine.

Use in patients treated with pioglitazone

While a causal relationship between dapagliflozin and bladder cancer is unlikely (see sections 4.8 and 5.3), as a precautionary measure, Qtrilmet is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Use with potent CYP3A4 inducers

Using CYP3A4 inducers like glucocorticoids, beta-2 agonists, diuretics, carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of Qtrilmet. Glycaemic control should be assessed, especially at the beginning, when it is used concomitantly with a potent CYP3A4/5 inducer (see section 4.5).

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Lactose

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have been performed with the individual active substances of Qtrilmet.

Pharmacodynamic interactions

Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Qtrilmet must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Combinations requiring precautions for use
Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products, and observed for loss

of blood glucose control or hypoglycaemia. If necessary, the dose of the glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Diuretics
Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Use with medicinal products known to cause hypoglycaemia
Saxagliptin and dapagliflozin can individually increase the risk of hypoglycaemia when combined with insulin or an insulin secretagogue. Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur during concomitant use with other glucose-lowering agents. Therefore, a lower dose of insulin or insulin secretagogue may be required to reduce the risk of hypoglycaemia when these agents are used in combination with Qtrilmet (see sections 4.4 and 4.8).

Pharmacokinetic interactions

Metformin
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Saxagliptin
The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5).

Dapagliflozin
The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by uridine diphosphate (UDP) glucuronosyltransferase 1A9 (UGT1A9).

Effect of other medicinal products on metformin, saxagliptin or dapagliflozin

Metformin
No clinically relevant interaction has been identified.

Saxagliptin
The coadministration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital, and phenytoin) has not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4/5 inducer.

Concomitant administration of saxagliptin with the potent CYP3A4/5 inducer rifampicin reduced C_{max} and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP-4 activity inhibition over a dose interval were not influenced by rifampicin (see section 4.4).

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44% and 34%, respectively. These pharmacokinetic effects are not clinically meaningful and do not require dose adjustment.

Concomitant administration of saxagliptin with the potent inhibitor of CYP3A4/5 ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively. These pharmacokinetic

effects are not clinically meaningful and do not require dose adjustment.

In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin nor its major metabolite were meaningfully altered by dapagliflozin, metformin, glibenclamide, pioglitazone, digoxin, diltiazem, simvastatin, omeprazole, antacids or famotidine.

Dapagliflozin
Following coadministration of dapagliflozin with rifampicin (an inducer of uridine 5'-diphospho-glucuronosyl transferase [UGT] and CYP3A4/5), a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin and phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT 1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion.

The pharmacokinetics of dapagliflozin were not meaningfully altered by saxagliptin, metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Effect of metformin, saxagliptin or dapagliflozin on other medicinal products

Metformin
Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with:
- inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin;
- inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin;
- inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration;
- inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these medicinal products are co-administered with metformin, as metformin plasma concentration may increase (see section 4.4).

Saxagliptin
Saxagliptin did not meaningfully alter the pharmacokinetics of dapagliflozin, metformin, glibenclamide (a CYP2C9 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), digoxin (a P-gp substrate), simvastatin (a CYP3A4 substrate), the active components of a combined oral contraceptive (ethinylestradiol and norgestimate), diltiazem or ketoconazole.

Dapagliflozin
In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of saxagliptin, metformin, pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin, glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of this medicinal product, or its components (metformin hydrochloride, saxagliptin and dapagliflozin) has not been studied in pregnant women. Studies in animals with saxagliptin have shown reproductive toxicity at high doses (see section 5.3). Studies with dapagliflozin in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

Qtrilmet should not be used during pregnancy. If pregnancy is detected, treatment with this medicinal product should be discontinued.

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Breast-feeding

Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded. It is unknown whether saxagliptin and dapagliflozin and/or their metabolites are excreted in human milk. Animal studies have shown excretion of saxagliptin and/or metabolite in milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in breast-feeding offspring (see section 5.3).

This medicinal product should not be used while breast-feeding.

Fertility

The effect of this medicinal product, or its components (metformin hydrochloride, saxagliptin and dapagliflozin) on fertility in humans has not been studied. Effects on fertility were observed using saxagliptin in male and female rats at high doses producing overt signs of toxicity (see section 5.3). In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Qtrilmet has no or negligible influence on the ability to drive and use machines.

When driving or using machines, it should be taken into account that dizziness has been reported in studies with saxagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia (e.g. insulin and sulphonylureas).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions associated with Qtrilmet are upper respiratory tract infections (very common), hypoglycaemia when used with SU (very common), gastrointestinal symptoms (very common) and urinary tract infections (common). Diabetic ketoacidosis may occur rarely and lactic acidosis may occur very rarely (see section 4.4).

The safety profile of the combined use of metformin, saxagliptin and dapagliflozin is comparable to the adverse reactions identified for the respective mono-components.

Tabulated list of adverse reactions

The safety profile is based on pooled analysis of three placebo controlled phase 3 clinical trials in 1,169 patients for up to 52 weeks, of which 492 patients received a combination of saxagliptin 5 mg, dapagliflozin 10 mg, plus metformin (see section 5.1). Additional safety data include clinical trials, post-authorisation safety studies and post-marketing experience with the mono-components. The adverse reactions associated with Qtrilmet are presented in Table 1. The adverse reactions are listed by system organ class (SOC) and frequency. Frequency categories were defined according to very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (≥ 1/100,000 to < 1/10,000) and not known (cannot be estimated from the available data).

Table 1. Compilation of adverse reactions for Qtrilmet

System organ class	Very common	Common[A]	Uncommon[B]	Rare	Very rare	Not known
Infections and infestations	Upper respiratory tract infection[¶1]	Urinary tract infection[#¶2], vulvo-vaginitis, balanitis and related genital infection[#3], gastro-enteritis[¶D]	Fungal infection[#]		Necrotising fasciitis of the perineum (Fournier's gangrene)[#,C,7]	
Immune system disorders			Hypersen-sitivity reactions[¶C]	Anaphyl-actic reactions including anaphylactic shock[¶C]		
Metabolism and nutrition disorders	Hypo-glycaemia[D#¶] (when used with SU)	Dyslipid-aemia[#4]	Volume depletion[#], thirst[#]	Diabetic ketoacidosis[#,H,7]	Lactic acidosis[§], Vitamin B_{12} deficiency[§G]	
Nervous system disorders		Headache[¶], dizziness[¶]				
Gastro-intestinal disorders	Gastro-intestinal symptoms[§F]	Dyspepsia[D¤] gastritis[D¤] taste disturbance[§]	Constipation[#], dry mouth[#], pancreatitis[¶C]			
Hepatobiliary disorders					Liver function disorders[§], hepatitis[§]	
Renal and urinary disorders		Dysuria[#], polyuria[#D,5]	Nocturia[#], renal impairment[#]			
Skin and subcutaneous tissue		Rash[#¶6]	Dermatitis[¶C], pruritus[¶C], urticaria[¶C]	Angio-edema[¶C]	Erythema[§]	Bullous pemphi-goid[C,7]

System organ class	Very common	Common[A]	Uncommon[B]	Rare	Very rare	Not known
disorders						
Musculo-skeletal and connective tissue disorders		Arthralgia[¤], back pain[#], myalgia[D ¤]				
Reproductive system and breast disorders			Erectile dysfunction[¤], pruritus genital[#], vulvovaginal pruritus[#]			
General disorders and administration site conditions		Fatigue[¶ D], oedema peripheral[¶ D]				
Investigations		Creatinine renal clearance decreased[#], haematocrit increased[# E]	Blood creatinine increased[#], blood urea increased[#], weight decreased[#]			

Adverse reaction reported for dapagliflozin.
¶ Adverse reaction reported for saxagliptin.
§ Adverse reaction reported for metformin.
¤ Adverse reaction reported for the combined use of saxagliptin and metformin.

A Adverse reactions, except for taste disturbance, reported in ≥ 2% of subjects treated with the combined use of saxagliptin + dapagliflozin + metformin in the pooled safety analysis, or if reported in < 2% in the pooled safety analysis, they were based on the individual mono-components data.
B Frequencies of all uncommon adverse reactions were based on the individual mono-components data.
C Adverse reaction originates from saxagliptin or dapagliflozin post-marketing surveillance data.
D Adverse reactions were reported in ≥ 2% of subjects with any of the mono-components, and ≥ 1% more than placebo, but not in the pooled safety analysis.
E Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
F Gastrointestinal symptoms (subsumed terms included nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite) occur most frequently during initiation of therapy and resolve spontaneously in most cases.
G Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency. Consideration of such etiology is recommended if a patient presents with megaloblastic anaemia.
H Reported in the dapagliflozin cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.
1 Upper respiratory tract infection includes the following preferred terms: nasopharyngitis, influenza, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, pharyngitis bacterial, tonsillitis, acute tonsillitis, laryngitis, viral pharyngitis, and viral upper respiratory tract infection.
2 Urinary tract infection includes the following preferred terms: urinary tract infection, *Escherichia* urinary tract infection, pyelonephritis, and prostatitis.
3 Vulvovaginitis, balanitis and related genital infection include the following preferred terms: vulvovaginal mycotic infection, balanoposthitis, genital infection fungal, vaginal infection, and vulvovaginitis.
4 Dyslipidaemia includes the following preferred terms: dyslipidaemia, hyperlipidaemia, hypercholesterolaemia, and hypertriglyceridaemia.
5 Polyuria includes the following preferred terms: polyuria, and pollakiuria.
6 Rash was reported during the postmarketing use of saxagliptin and dapagliflozin. Preferred terms reported in dapagliflozin clinical trials included in order of frequency: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous.

[7] See section 4.4.

Description of selected adverse reactions

Hypoglycaemia

In the pooled safety analysis, the overall incidence of hypoglycaemia (all reported events including those with central laboratory FPG ≤ 3.9 mmol/L) was 2.0% in subjects treated with dapagliflozin 10 mg and saxagliptin 5 mg plus metformin (combination therapy), 0.6% in the saxagliptin plus metformin group, and 2.3% in the dapagliflozin plus metformin group.

In a 24-week study comparing the combination of saxagliptin and dapagliflozin plus metformin with or without SU, with insulin plus metformin with or without SU, the overall incidence rates for hypoglycaemia in patients without a background treatment of SU, were 12.7% for the combination compared to 33.1% for insulin. The overall incidence rates of hypoglycaemia in two 52-week studies comparing the combination therapy to glimepiride (SU) were: for the 1st study, 4.2% for the combination therapy versus 27.9% for glimepiride plus metformin versus 2.9% for dapagliflozin plus metformin; for the 2nd study, 18.5% for the combination therapy versus 43.1% for glimepiride plus metformin.

Volume depletion

In the pooled safety analysis, events related to volume depletion (hypotension, dehydration, and hypovolemia) were reflective of the adverse events with dapagliflozin and were reported in two subjects (0.4%) in the saxagliptin plus dapagliflozin plus metformin group (serious adverse event [SAE] of syncope and an AE of urine output decreased), and 3 subjects (0.9%) in the dapagliflozin plus metformin group (2 AEs of syncope and 1 of hypotension).

Decreased renal function

Metformin/saxagliptin/dapagliflozin combination: In the pooled safety analysis for Qtrilmet, the incidence of adverse events related to decreased renal function was 2.0% subjects in the saxagliptin plus dapagliflozin plus metformin group, 1.8% subjects in the saxagliptin plus metformin group, and 0.6% subjects in the dapagliflozin plus metformin group. Subjects with adverse events of renal impairment had lower mean eGFR values at baseline of 61.8 mL/min/1.73 m^2 compared to 93.6 mL/min/1.73 m^2 in the overall population. The majority of events were considered non-serious, mild or moderate in intensity, and resolved. The change in mean eGFR from baseline at week 24 was -1.17 mL/min/1.73 m^2 in the saxagliptin plus dapagliflozin plus metformin group, -0.46 mL/min/1.73 m^2 in saxagliptin plus metformin, and 0.81 mL/min/1.73 m^2 in dapagliflozin plus metformin.

Dapagliflozin: Adverse reactions related to increased creatinine have been reported for dapagliflozin as a mono-component. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Vulvovaginitis, balanitis and related genital infections

The reported adverse reactions of vulvovaginitis, balanitis and related genital infections from pooled safety analysis were reflective of the safety profile of dapagliflozin. Adverse reactions of genital infection were reported in 3.0% in the saxagliptin plus dapagliflozin plus metformin group, 0.9% of saxagliptin plus metformin group and 5.9% of subjects in the dapagliflozin plus metformin group. The majority of the genital infection adverse reactions were reported in females (84% of subjects with a genital infection), were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported post-marketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Diabetic ketoacidosis

In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

Urinary tract infections

In the pooled safety analysis, urinary tract infections (UTIs) were balanced across the 3 treatment groups: 5.7% in the saxagliptin plus dapagliflozin plus metformin group, 7.4% in the saxagliptin plus metformin group, and 5.6% in the dapagliflozin plus metformin group. One patient in the saxagliptin plus dapagliflozin plus metformin group experienced an SAE of pyelonephritis and discontinued treatment. The majority of the urinary tract infections were reported in females (81% of subjects with UTI), were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Malignancies

Saxagliptin/dapagliflozin combination: Malignant and unspecified neoplasms were reported in 3 subjects included in the pooled safety analysis. They included adverse events of gastric neoplasm, pancreatic cancer with hepatic metastases, and invasive ductal breast carcinoma in the saxagliptin plus dapagliflozin plus metformin group. Considering the short latency between first drug exposure and tumour diagnosis, a causal relationship to any specific tumour type is considered unlikely.

Dapagliflozin: In the 21-study active- and placebo-controlled pool, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50%) and placebo/comparator (1.50%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). 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 (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. The numerical imbalance of breast, bladder, and prostate tumours must be considered with caution; it will be further investigated in post-authorisation studies.

Laboratory findings

Decrease in lymphocyte counts
Saxagliptin: Across clinical studies in the saxagliptin programme a small decrease in absolute lymphocyte count was observed, approximately 100 cells/microL relative to placebo. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. This decrease in mean absolute lymphocyte count was not associated with clinically relevant adverse reactions.

Lipids

Data from the saxagliptin and dapagliflozin plus metformin treatment arms of the three individual studies included in the pooled analysis, demonstrated trends of mean percent increases from baseline (rounded to the nearest tenth) in total cholesterol (Total C), (ranging from 0.4% to 3.8%), LDL-C (ranging from 2.1% to 6.9%), and HDL-C (ranging 2.3% to 5.2%) along with mean percent decreases from baseline in triglycerides (ranging from -3.0% to -10.8%).

Special populations

Elderly

Of the 1,169 subjects treated in the pooled safety data from the 3 clinical trials, 1,007 subjects (86.1%) were aged < 65 years, 162 subjects (13.9%) were aged ≥ 65 years and 9 subjects (0.8%) were aged ≥ 75 years. Generally, the most common adverse events reported in ≥ 65 years old were similar to < 65 years old. Therapeutic experience in patients 65 years and older is limited, and very limited in patients 75 years and older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by haemodialysis (23% of dose over four hours). The removal of dapagliflozin by haemodialysis has not been studied. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD25.

Mechanism of action

Qtrilmet combines three anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: metformin hydrochloride, a member of the biguanide class, saxagliptin, a DPP-4 inhibitor and dapagliflozin, a SGLT2 inhibitor.

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore, does not produce hypoglycaemia. Metformin may act via three mechanisms; by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle, and by delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Saxagliptin is a highly potent (K_i: 1.3 nM), selective, reversible and competitive inhibitor of DPP-4, an enzyme responsible for the breakdown of incretin hormones. This results in a glucose-dependent increase in insulin secretion, thus reducing fasting and post-prandial blood glucose concentrations.

Dapagliflozin is a highly potent (K_i: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). Dapagliflozin blocks reabsorption of filtered glucose from the S1 segment of the renal tubule, effectively lowering blood glucose in a glucose dependent and insulin-independent manner. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. The increased urinary glucose excretion with SGLT2 inhibition produces an osmotic diuresis, and can result in a reduction in systolic BP.

Clinical efficacy and safety

The safety and efficacy of the fixed-dose combination of metformin/saxagliptin/dapagliflozin was evaluated in five randomised, double-blind, active/placebo-controlled clinical trials in adult subjects with type 2 diabetes mellitus. Two add-on therapy trials, which added either dapagliflozin to saxagliptin plus metformin or saxagliptin to dapagliflozin plus metformin, were conducted for 24 weeks followed by a 28-week extension treatment period. In one trial conducted for 24 weeks, saxagliptin and dapagliflozin added to metformin was compared to saxagliptin or dapagliflozin added to metformin. In one of two supportive studies, therapy with saxagliptin and dapagliflozin was compared to glimepiride in patients inadequately controlled on metformin. The other study compared therapy with saxagliptin and dapagliflozin to insulin glargine in patients inadequately controlled on metformin with or without a sulphonylurea.

Glycaemic control

Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin

A 24-week randomised, double-blind, placebo-controlled study with a 28-week extension compared the sequential addition of 10 mg dapagliflozin to 5 mg saxagliptin and metformin to the addition of placebo to 5 mg saxagliptin (DPP-4 inhibitor) and metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5%). Three hundred twenty (320) patients were randomised equally into either the dapagliflozin added to saxagliptin plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group. The treatment groups were proportionally well balanced with regard to demographics, subject characteristics, disease characteristics, and medical history. The mean age was 55.1 years and 54.4% of patients were female. The mean duration of T2DM when entering the study was 7.6 years, mean baseline HbA1c of 8.2%. All patients had been on a stable dose of metformin (1,500 mg or greater per day) for at least 8 weeks prior to screening visit. 101 patients were on a maximum dose of DPP4 inhibitor for at least 8 weeks before the screening visit and then switched to saxagliptin 5 mg for 8 weeks ahead of the study start. The remaining 219 patients started to take 5 mg saxagliptin 16 weeks ahead of the study start.

The group with dapagliflozin sequentially added to saxagliptin and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see Table 2). The effect in HbA1c observed at week 24 was sustained at week 52. The adjusted mean changes from baseline in HbA1c for the dapagliflozin and saxagliptin plus metformin and placebo and saxagliptin plus metformin groups were -0.74% (95% CI: -0.90, -0.57) and 0.07% (95% CI: -0.13, 0.27), respectively. The difference in the adjusted mean change from baseline to week 52 between the treatment groups was -0.81% (95% CI: -1.06, -0.55).

Add-on therapy with saxagliptin in patients inadequately controlled on dapagliflozin plus metformin

A 24-week randomised, double-blind, placebo-controlled study conducted on patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5%) on metformin and dapagliflozin alone, compared the sequential addition of 5 mg saxagliptin to 10 mg dapagliflozin and metformin, to the addition of placebo to 10 mg dapagliflozin and metformin. 153 patients were

randomised into the saxagliptin added to dapagliflozin plus metformin treatment group, and 162 patients were randomised into the placebo added to dapagliflozin plus metformin treatment group. The treatment groups were proportionally well balanced with regard to demographics, subject characteristics, disease characteristics, and medical history. The mean age was 54.6 years and 52.7% of patients were female. The mean duration of T2DM when entering the study was 7.7 years, mean baseline HbA1c of 7.9%. Patients had been on a stable dose of metformin (1,500 mg or greater per day) for at least 8 weeks prior to screening visit and were then treated with metformin and dapagliflozin 10 mg for 10 weeks ahead of the study start.

The group with saxagliptin 5 mg sequentially added to dapagliflozin 10 mg and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to dapagliflozin plus metformin group at 24 weeks (see Table 2). The effect in HbA1c observed at week 24 was sustained at week 52. At week 52, adjusted mean changes from baseline in HbA1c in the saxagliptin and dapagliflozin plus metformin and placebo and dapagliflozin plus metformin groups were -0.38% (95% CI: -0.53, -0.22) and 0.05% (95% CI: -0.11, 0.20), respectively. The difference in the adjusted mean change from baseline to week 52 between the treatment groups was -0.42% [95% CI: -0.64, -0.20].

Table 2. HbA1c change from baseline at week 24 excluding data after rescue for randomised subjects – studies MB102129 and CV181168

Efficacy parameter	Sequential add-on clinical trials			
	Study MB102129		Study CV181168	
	Dapagliflozin 10 mg added to saxagliptin 5 mg + metformin (N=160) †	Placebo + saxagliptin 5 mg + metformin (N=160) †	Saxagliptin 5 mg added to dapagliflozin 10 mg + metformin (N=153) †	Placebo + dapagliflozin 10 mg + metformin (N=162) †
HbA1c (%) at week 24 *				
Baseline (mean)	8.24	8.16	7.95	7.85
Change from baseline (adjusted mean‡) (95% CI)	-0.82 (-0.96, 0.69)	-0.10 (-0.24, 0.04)	-0.51 (-0.63, -0.39)	-0.16 (-0.28, -0.04)
Difference in HbA1c effect				
Adjusted mean (95% CI) p-value	-0.72 (-0.91, -0.53) < 0.0001		-0.35 (-0.52, -0.18) < 0.0001	

* LRM = Longitudinal repeated measures (using values prior to rescue).
† N is the number of randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.

Proportion of patients achieving HbA1c < 7% in study MB102129 and study CV181168
The proportion of patients achieving HbA1c < 7.0% at week 24 in the add-on therapy with dapagliflozin 10 mg to saxagliptin 5 mg plus metformin trial was higher in the dapagliflozin 10 mg and saxagliptin 5 mg plus metformin group 38.0% (95% CI [30.9, 45.1]) compared to the placebo plus saxagliptin 5 mg plus metformin group 12.4% (95% CI [7.0, 17.9]). The effect in HbA1c observed at week 24 was sustained at week 52. The adjusted percent of subjects with HbA1c < 7.0% at week 52 was 29.4% in the dapagliflozin and saxagliptin plus metformin group and 12.6% in the placebo and

saxagliptin plus metformin group. The adjusted percent difference at week 52 between the treatment groups was 16.8%.

The proportion of patients achieving HbA1c < 7% at week 24 for add-on therapy with saxagliptin 5 mg to dapagliflozin 10 mg plus metformin trial was higher in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group 35.3% (95% CI [28.2, 42.2]) compared to the placebo plus dapagliflozin 10 mg plus metformin group 23.1% (95% CI [16.9, 29.3]). The effect in HbA1c observed at week 24 was sustained at week 52. The adjusted percent of subjects with HbA1c < 7.0% at week 52 was 29.3% in the saxagliptin and dapagliflozin plus metformin group and 13.1% in the placebo and dapagliflozin plus metformin group. The adjusted percent difference at week 52 between the treatment groups was 16.2%.

Therapy with saxagliptin 5 mg and dapagliflozin 10 mg in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%), participated in this 24-week randomised, double-blind, active comparator-controlled superiority trial to compare the combination of saxagliptin 5 mg and dapagliflozin 10 mg added concurrently to metformin, versus saxagliptin 5 mg (DPP-4 inhibitor) or dapagliflozin 10 mg (SGLT2 inhibitor) added to metformin. The treatment groups were proportionally well balanced with regard to demographics, subject characteristics, disease characteristics, and medical history. The mean age was 53.8 years and 49.8% of patients were female. The mean duration of T2DM when entering the study was 7.6 years, mean baseline HbA1c of 8.94% and patients had been on a stable dose of metformin (1,500 mg or greater per day) for at least 8 weeks prior to the screening visit. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin, saxagliptin 5 mg and placebo added to metformin, or dapagliflozin 10 mg and placebo added to metformin.

The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 3).

Table 3. HbA1c at week 24 in active-controlled study comparing the combination of saxagliptin 5 mg and dapagliflozin 10 mg added concurrently to metformin with either saxagliptin 5 mg or dapagliflozin 10 mg added to metformin

Efficacy parameter	**Saxagliptin 5 mg + dapagliflozin 10 mg + metformin N=179†**	**Saxagliptin 5 mg + metformin N=176†**	**Dapagliflozin 10 mg + metformin N=179†**
HbA1c (%) at week 24*			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean‡) (95% Confidence interval [CI])	-1.47 (-1.62, -1.31)	-0.88 (-1.03, -0.72)	-1.20 (-1.35, -1.04)
Difference from saxagliptin + metformin (adjusted mean‡) (95% CI)	-0.59§ (-0.81, -0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean‡) (95% CI)	-0.27¶ (-0.48, -0.05)	-	-

***** LRM = Longitudinal repeated measures using values prior to rescue.
† Randomised and treated patients.
‡ Least squares mean adjusted for baseline value.

§ p-value < 0.0001.
¶ p-value = 0.0166.

The majority of patients in this study had a baseline HbA1c of > 8% (see Table 4). The combination of saxagliptin 5 mg and dapagliflozin 10 mg added to metformin consistently demonstrated greater reductions in HbA1c irrespective of baseline HbA1c compared with saxagliptin 5 mg or dapagliflozin 10 mg alone added to metformin. In a separate pre-specified subgroup analysis, mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values.

Table 4. HbA1c subgroup analysis by baseline HbA1c at week 24 in randomised subjects

Treatments	**Adjusted mean change from baseline by baseline HbA1c**		
	< 8.0%	**≥ 8% to < 9.0%**	**≥ 9.0%**
Saxagliptin + Dapagliflozin + Metformin Adjusted mean change from baseline (95% CI)	-0.80 (n=37) (-1.12, -0.47)	-1.17 (n=56) (-1.44, -0.90)	-2.03 (n=65) (-2.27, -1.80)
Saxagliptin + Metformin Adjusted mean change from baseline (95% CI)	-0.69 (n=29) (-1.06, –0.33)	-0.51 (n=51) (-0.78, -0.25)	-1.32 (n=63) (-1.56, -1.09)
Dapagliflozin + Metformin Adjusted mean change from baseline (95% CI)	-0.45 (n=37) (-0.77, -0.13)	-0.84 (n=52) (-1.11, -0.57)	-1.87 (n=62) (-2.11, -1.63)

n = number of subjects with non-missing baseline and a week 24 value.

Proportion of patients achieving HbA1c < 7%
41.4% (95% CI [34.5, 48.2]) of patients in the saxagliptin 5 mg and dapagliflozin 10 mg combination group achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) patients in the saxagliptin 5 mg group and 22.2% (95% CI [16.1, 28.3]) patients in the dapagliflozin 10 mg group at week 24.

Therapy with saxagliptin 5 mg and dapagliflozin 10 mg in comparison to glimepiride in patients inadequately controlled on metformin

A 52-week randomised, double-blind, active-controlled, parallel-group study with a blinded 104-week extension compared once daily saxagliptin 5 mg and dapagliflozin 10 mg plus metformin to glimepiride (a sulphonylurea) up-titrated 1-6 mg plus placebo with metformin in T2DM patients with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 10.5%) on metformin alone. Patients on glimepiride/placebo dose were up-titrated starting at 1 mg per day over 12 weeks to optimal glycaemic effect (FPG < 6.1 mmol/L) or the highest tolerable dose. Thereafter, glimepiride/placebo dose were kept constant, except for down-titration to prevent hypoglycaemia.

At week 52, the adjusted mean change in HbA1c from baseline was -1.35% for the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (N=218), compared to -0.98% for the glimepiride plus metformin group (N=212) (difference -0.37%, 95% CI [-0.57, -0.18], p < 0.001).

Therapy with saxagliptin 5 mg and dapagliflozin 10 mg in comparison to insulin glargine in patients inadequately controlled on metformin with or without a sulphonylurea

A 24-week randomised, open-label, active-controlled, parallel-group study with a 28-week extension compared orally once daily saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulphonylurea to titrated subcutaneous insulin glargine plus metformin with or without a sulphonylurea in T2DM patients with inadequate glycaemic control (HbA1c ≥ 8.0% and ≤ 12.0%).

At week 24, the adjusted mean change in HbA1c from baseline was -1.67% for the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU group (N=319), which was noninferior to the change of -1.54% in the insulin glargine plus metformin with or without SU group (N=312) (difference -0.13%, 95% CI [-0.30, 0.03]).

Body weight

Combination therapy with saxagliptin 5 mg and dapagliflozin 10 mg compared to glimepiride in T2DM patients with inadequate glycaemic control on metformin alone resulted in significant difference in mean body weight change at week 52. The adjusted mean change from baseline was -3.11 kg (95% CI [-3.65, -2.57]) for the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group, and 0.95 kg (95% CI [0.38, 1.51]) for the glimepiride plus metformin group. The difference in mean body weight between treatment groups was -4.06 kg (95% CI [-4.84, -3.28] p < 0.001) at week 52.

The combination of saxagliptin 5 mg and dapagliflozin 10 mg plus metformin, with or without a sulphonylurea group, compared to treatment with insulin glargine and metformin, with or without a SU, resulted in significant difference in body weight change at week 24. The mean change from baseline was -1.50 kg (95% CI [-1.89, -1.11]) for the saxagliptin 5 mg and dapagliflozin 10 mg, plus metformin group, versus 2.14 kg (95% CI [1.75, 2.54]) in the insulin glargine plus metformin group. The difference in mean body weight between treatment groups was -3.64 kg (95% CI [-4.20, -3.09] p < 0.001).

In the study of concomitant addition of saxagliptin and dapagliflozin, the adjusted mean change from baseline in body weight at week 24 (excluding data after rescue) was -2.05 kg (95% CI [-2.52, -1.58]) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group and -2.39 kg (95% CI [-2.87, -1.91]) in the dapagliflozin 10 mg plus metformin group, while the saxagliptin 5 mg plus metformin group had no change (0.00 kg) (95% CI [-0.48, 0.49]).

Blood pressure

In study MB102129 and study CV181168, treatment with Qtrilmet resulted in change from baseline for systolic blood pressure ranging from -1.3 to -2.2 mmHg and for diastolic blood pressure ranging from -0.5 to -1.2 mmHg caused by Qtrilmet's mild diuretic effect. The modest lowering effects on BP were consistent over time and a similar number of patients had systolic BP < 130 mmHg or diastolic BP < 80 mmHg at week 24 across the treatment groups.

In the study comparing concomitant therapy of saxagliptin and dapagliflozin with glimepiride in patients inadequately controlled on metformin alone, the decrease in systolic blood pressure at week 52 in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (-2.6 mmHg 95% CI [-4.4, -0.8]) was greater than in the glimepiride plus metformin group (1.0 mmHg 95% CI [-0.9, 2.9]). The difference in mean SBP between treatment groups was -3.6 mmHg (95% CI [-6.3, -1.0] p = 0.007).

Cardiovascular safety

In the pooled safety analysis, cardiovascular (CV) events that were adjudicated and confirmed as CV events were reported in a total of 1.0% of subjects in the saxagliptin plus dapagliflozin plus metformin group, 0.6% in the saxagliptin plus metformin group, and 0.9% in the dapagliflozin plus metformin group.

Metformin
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p = 0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p = 0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p = 0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p = 0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p = 0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p = 0.01).

Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus - thrombolysis in myocardial infarction (SAVOR) study
SAVOR was a CV outcome trial in 16,492 patients with HbA1c ≥ 6.5% and < 12% (12,959 with established CV disease; 3,533 with multiple risk factors only) who were randomised to saxagliptin (n=8,280) or placebo (n=8,212) added to regional standards of care for HbA1c and CV risk factors. The study population included those ≥ 65 years (n = 8,561) and ≥ 75 years (n = 2,330), with normal or mild renal impairment (n = 13,916) as well as moderate (n = 2,240) or severe (n = 336) renal impairment.

The primary safety (non-inferiority) and efficacy (superiority) endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

After a mean follow up of 2 years, the trial met its primary safety endpoint demonstrating saxagliptin does not increase the cardiovascular risk in patients with type 2 diabetes compared to placebo when added to current background therapy.

No benefit was observed for MACE or all-cause mortality.

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance favouring placebo [HR=1.27; (95% CI 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure, such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

Another secondary endpoint, all-cause mortality, occurred at a rate of 5.1% in the saxagliptin group and 4.6% in the placebo group. CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR = 1.27; (95% CI 1.00, 1.62); P = 0.051].

Dapagliflozin
A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 34.4% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9% had hypertension. The hazard ratio comparing dapagliflozin to comparator was 0.79 (95% CI: 0.58, 1.07), indicating that in this analysis dapagliflozin is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI, and stroke were observed with a hazard ratio of 0.77 (95% CI: 0.54, 1.10).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Qtrilmet in all subsets of the paediatric population in the treatment of type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Bioequivalence has been confirmed between Qtrilmet tablets and the individual components (metformin modified-release, saxagliptin and dapagliflozin) in healthy subjects when administered in the fed state.

Absorption

Metformin: Following a single oral dose of metformin extended-release tablet, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Saxagliptin: Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations (C_{max}) of saxagliptin and its major metabolite attained within 2 and 4 hours (T_{max}), respectively. The C_{max} and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its major metabolite were 78 ng h/mL and 214 ng h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

Dapagliflozin: Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food has relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreases dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Metformin: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63-276 L.

Saxagliptin: The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g. renal or hepatic impairment) are not expected to alter the disposition of saxagliptin. The volume of distribution of saxagliptin was 205 L.

Dapagliflozin: Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 L.

Biotransformation

Metformin: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Saxagliptin: The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major active metabolite of saxagliptin, 5-OH-saxagliptin, is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9 or 3A4.

Dapagliflozin: Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Elimination

Metformin: Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

Saxagliptin: The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours, respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36% and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion.

Dapagliflozin: The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin.

Linearity

Metformin: At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2,000 mg administered once daily.

Saxagliptin: The C_{max} and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Dapagliflozin: Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Special populations

Renal impairment

Metformin: The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased, leading to increased levels of metformin in plasma, (see sections 4.2, 4.3 and 4.4).

Saxagliptin: After a single dose of saxagliptin in subjects with mild, moderate or severe renal impairment (or ESRD) classified on the basis of creatinine clearance the mean AUC values of saxagliptin were 1.2-, and up to 2.1- and 4.5- fold higher, respectively, than AUC values in subjects with normal renal function. The AUC values of 5-OH-saxagliptin were also increased. The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite.

Dapagliflozin: At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Saxagliptin: In subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 (saxagliptin metabolite) were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects.

Dapagliflozin: In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B) mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Elderly

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see sections 4.2 and 4.4).

Saxagliptin: Elderly patients (65–80 years) had about 60% higher saxagliptin AUC than young patients (18–40 years). This is not considered clinically meaningful.

Dapagliflozin: There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Gender

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the anti-hyperglycaemic effect of metformin was comparable in males and females.

Saxagliptin: Females had approximately 25% higher systemic exposure values for saxagliptin. There were no clinically relevant differences observed in saxagliptin pharmacokinetics between males and females.

Dapagliflozin: The mean dapagliflozin AUC_{ss} in females was estimated to be about 22% higher than in males.

Race

Metformin hydrochloride: No studies of metformin pharmacokinetic parameters according to race have been performed.

Saxagliptin: Race was not identified as a statistically significant covariate on the apparent clearance of saxagliptin and its metabolite.

Dapagliflozin: There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight

Saxagliptin: Body weight had a small and non-clinically meaningful impact on saxagliptin exposure. Females had approximately 25% higher systemic-exposure values for saxagliptin, this difference is considered not clinically relevant.

Dapagliflozin: Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high-weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

Non-clinical studies of either metformin, saxagliptin or dapagliflozin revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity or carcinogenicity.

Saxagliptin: Saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) in cynomolgus monkeys. The no observed effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite, respectively, at the recommended human dose (RHD) of 5 mg/day. The clinical relevance of the skin lesions is not known, and skin lesions have not been observed in humans.

Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. The effect on offspring body weights were noted until

postnatal day 92 and 120 in females and males, respectively.

No non-clinical studies have been conducted in metformin/saxagliptin/dapagliflozin combination.

Reproductive and developmental toxicity

Metformin: Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

Saxagliptin: Saxagliptin has effects on fertility in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

Dapagliflozin: Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations (with dose-related increases in kidney weight and macroscopic kidney enlargement) were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

Dapagliflozin dosed to maternal rats from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (at maternal and pup dapagliflozin exposures of 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose [MRHD]). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (pup exposures ≥ 29 times the human values at the MRHD). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The NOAEL for developmental toxicity is associated with a maternal systemic exposure 19 times the human values at the MRHD.

In additional studies of embryo-foetal development in rabbits, dapagliflozin caused neither maternal nor developmental toxicities at any dose tested; the highest dose tested corresponded to a systemic exposure 1,191 times the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the human values at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Carmellose sodium (E466)

Crospovidone (E1202)
Hypromellose (E464)
Lactose
Magnesium stearate (E470b)
Cellulose, microcrystalline (E460i)
Silica, dental type (E551)

Film-coating

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets
Macrogol (E1521)
Poly(vinyl alcohol) (E1203)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets
Macrogol (E1521)
Poly(vinyl alcohol) (E1203)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide black (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PCTFE/alu blister
Shelf life: 2 years

PA/alu/PVC/alu blister
Shelf life: 30 months

6.4 Special precautions for storage

PVC/PCTFE/alu blister
Do not store above 30°C.

PA/alu/PVC/alu blister
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/alu blister
Pack size of 14, 28, 56 and 196 modified-release tablets in calendar blisters.
Pack size of 14, 28, 56, 60 and 196 modified-release tablets in blisters.

PA/alu/PVC/alu blister
Pack size of 14, 28, 56, 60 and 196 modified-release tablets in blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets

PVC/PCTFE/alu blister
EU/1/19/1401/001 14 modified-release tablets
EU/1/19/1401/002 28 modified-release tablets
EU/1/19/1401/003 56 modified-release tablets
EU/1/19/1401/004 60 modified-release tablets
EU/1/19/1401/005 196 modified-release tablets
EU/1/19/1401/006 14 modified-release tablets (calendar blister)
EU/1/19/1401/007 28 modified-release tablets (calendar blister)
EU/1/19/1401/008 56 modified-release tablets (calendar blister)
EU/1/19/1401/009 196 modified-release tablets (calendar blister)

PA/alu/PVC/alu blister
EU/1/19/1401/010 14 modified-release tablets
EU/1/19/1401/011 28 modified-release tablets
EU/1/19/1401/012 56 modified-release tablets
EU/1/19/1401/013 60 modified-release tablets
EU/1/19/1401/014 196 modified-release tablets

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets

PVC/PCTFE/alu blister
EU/1/19/1401/015 14 modified-release tablets
EU/1/19/1401/016 28 modified-release tablets
EU/1/19/1401/017 56 modified-release tablets
EU/1/19/1401/018 60 modified-release tablets
EU/1/19/1401/019 196 modified-release tablets
EU/1/19/1401/020 14 modified-release tablets (calendar blister)
EU/1/19/1401/021 28 modified-release tablets (calendar blister)
EU/1/19/1401/022 56 modified-release tablets (calendar blister)
EU/1/19/1401/023 196 modified-release tablets (calendar blister)

PA/alu/PVC/alu blister
EU/1/19/1401/024 14 modified-release tablets
EU/1/19/1401/025 28 modified-release tablets
EU/1/19/1401/026 56 modified-release tablets
EU/1/19/1401/027 60 modified-release tablets
EU/1/19/1401/028 196 modified-release tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union references dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets
metformin hydrochloride/saxagliptin/dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 850 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release tablets

14 modified-release tablets
28 modified-release tablets
56 modified-release tablets
60 modified-release tablets
196 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

PVC/PCTFE/alu blister:

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

PVC/PCTFE/alu blister:
EU/1/19/1401/001 14 modified-release tablets
EU/1/19/1401/002 28 modified-release tablets
EU/1/19/1401/003 56 modified-release tablets
EU/1/19/1401/004 60 modified-release tablets
EU/1/19/1401/005 196 modified-release tablets
EU/1/19/1401/006 14 modified-release tablets (calendar blister)
EU/1/19/1401/007 28 modified-release tablets (calendar blister)
EU/1/19/1401/008 56 modified-release tablets (calendar blister)
EU/1/19/1401/009 196 modified-release tablets (calendar blister)

PA/alu/PVC/alu blister:
EU/1/19/1401/010 14 modified-release tablets
EU/1/19/1401/011 28 modified-release tablets
EU/1/19/1401/012 56 modified-release tablets
EU/1/19/1401/013 60 modified-release tablets
EU/1/19/1401/014 196 modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Qtrilmet 850 mg/2.5 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 850 mg/2.5 mg/5 mg tablets
metformin HCl/saxagliptin/dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 850 mg/2.5 mg/5 mg tablets
metformin HCl/saxagliptin/dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets
metformin hydrochloride/saxagliptin/dapagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1,000 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release tablets

14 modified-release tablets
28 modified-release tablets
56 modified-release tablets
60 modified-release tablets
196 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

PVC/PCTFE/alu blister:

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

PVC/PCTFE/alu blister:
EU/1/19/1401/015 14 modified-release tablets
EU/1/19/1401/016 28 modified-release tablets
EU/1/19/1401/017 56 modified-release tablets
EU/1/19/1401/018 60 modified-release tablets
EU/1/19/1401/019 196 modified-release tablets
EU/1/19/1401/020 14 modified-release tablets (calendar blister)
EU/1/19/1401/021 28 modified-release tablets (calendar blister)
EU/1/19/1401/022 56 modified-release tablets (calendar blister)
EU/1/19/1401/023 196 modified-release tablets (calendar blister)

PA/alu/PVC/alu blister:
EU/1/19/1401/024 14 modified-release tablets
EU/1/19/1401/025 28 modified-release tablets
EU/1/19/1401/026 56 modified-release tablets
EU/1/19/1401/027 60 modified-release tablets
EU/1/19/1401/028 196 modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Qtrilmet 1,000 mg/2.5 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 1,000 mg/2.5 mg/5 mg tablets
metformin HCl/saxagliptin/dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Qtrilmet 1,000 mg/2.5 mg/5 mg tablets
metformin HCl/saxagliptin/dapagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets
Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets
metformin hydrochloride/saxagliptin/dapagliflozin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Qtrilmet is and what it is used for
2. What you need to know before you take Qtrilmet
3. How to take Qtrilmet
4. Possible side effects
5. How to store Qtrilmet
6. Contents of the pack and other information

1. What Qtrilmet is and what it is used for

Qtrilmet contains the active substances metformin, saxagliptin, and dapagliflozin. Each belongs to a group of medicines called "oral anti-diabetics". This medicine is taken by mouth to treat diabetes and each of the active substances works in a different way to treat the condition.

This medicine is for a type of diabetes called "type 2 diabetes". If you have type 2 diabetes, your pancreas does not make enough insulin or your body is not able to use the insulin it produces properly. This leads to a high level of sugar (glucose) in your blood. The three medicines in Qtrilmet lower the amount of sugar in the blood by causing it to be taken up into cells or passed out of the body in the urine.

Qtrilmet is only given to adults aged 18 years and older. It is used if other oral diabetes medicines, along with diet and exercise, cannot control your diabetes well enough. It is taken on its own, or it can be combined with a different type of diabetes medicine called a sulphonylurea.

2. What you need to know before you take Qtrilmet

Do not take Qtrilmet:
- if you are allergic to metformin, saxagliptin, dapagliflozin, or any of the other ingredients of this medicine (listed in section 6);
- if you have had a serious allergic reaction to some other medicines used to control your blood sugar, namely:
  - 'gliptins' (or DPP-4 inhibitors) – like alogliptin, linagliptin and sitagliptin or,
  - 'gliflozins' (or SGLT2 inhibitors) – like canagliflozin and empagliflozin;
- if you have uncontrolled diabetes, with:
  - severe hyperglycaemia (very high blood glucose),
  - nausea, vomiting, diarrhoea, rapid weight loss,
  - lactic acidosis (see "Risk of lactic acidosis" below),

- ketoacidosis, where substances called 'ketone bodies' build up in the blood and which can lead to a diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness, or your breath developing an unusual fruity smell;
- if you have ever had a diabetic coma;
- if you have severely reduced kidney function;
- if you have a severe infection;
- if you have lost a lot of water from your body (dehydration) – due to long-lasting or severe diarrhoea, or if you have vomited several times in a row (see "Warnings and precautions" below);
- if you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing;
- if you have problems with your liver;
- if you drink large amounts of alcohol, either every day or only from time to time (please see section "Qtrilmet with alcohol").

Do not take Qtrilmet if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking Qtrilmet.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Qtrilmet, and during treatment:
- if you experience vomiting, stomach ache (abdominal pain), muscle cramps, a general feeling of not being well with severe tiredness, difficulty breathing, reduced body temperature or slow heartbeat. These may be symptoms of a very rare, but very serious side effect called **lactic acidosis** which can occur with Qtrilmet, particularly if your kidneys are not working properly. The risk of lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems, and medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). **Stop taking Qtrilmet and contact a doctor or go to the nearest hospital immediately if you experience symptoms of lactic acidosis**, as this condition is a medical emergency that may lead to coma;
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat. These may be symptoms of another rare, but very serious, sometimes life-threatening condition called **diabetic ketoacidosis.** With this condition, the levels of substances called "ketone bodies" increase in your urine or blood and this can be picked up in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or major surgery or serious illness (which increase the body's needs for insulin). **Stop taking Qtrilmet and contact a doctor or go to the nearest hospital immediately if you experience some of the symptoms of diabetic ketoacidosis, as this condition is a medical emergency;**
- if you lose a lot of body fluids, such as with severe vomiting, diarrhoea, fever, nausea (feeling sick), increased sweating in heat, or if you are not able to eat or drink. **Stop taking Qtrilmet for a short time if you have a condition that leads to dehydration** and talk to your doctor about what to do and when to start taking Qtrilmet again;
- if you have "type 1 diabetes". Qtrilmet should not be used to treat this condition;
- if you have or have had a disease of the pancreas;
- if you have reduced kidney function or liver problems;
- if your body's ability to fight infections (immunity) is reduced, such as with a disease like AIDS or from medicines that you take after an organ transplant;
- if you have ever had a serious hypersensitivity (allergic) reaction or your doctors have told you that you may have had one;
- if you have or have had serious heart disease;

- if you have risk factors for developing heart failure, such as problems with your kidneys. Your doctor will advise you of the signs and symptoms of heart failure. Symptoms can include shortness of breath, rapid increase in weight, and swelling of the ankles or feet (pedal oedema). Watch out for these symptoms and call your doctor, pharmacist, or nurse immediately if you get any of them;
- if you have or have had low blood pressure (hypotension);
- if you have very high levels of sugar in your blood which may make you dehydrated (lose too much body fluid). Possible signs of dehydration are listed in section 4. Tell your doctor before you start taking Qtrilmet if you have any of these signs;
- if you often get infections of the urinary tract or have a serious infection of the urinary tract, including urosepsis or pyelonephritis, which can cause fever, chills, burning sensation when passing water (urinating), blood in urine, and pain in your back or side. You should call your doctor, pharmacist, or nurse immediately if you experience any of these symptoms;
- if you have severe joint pain;
- if you take pioglitazone to lower your blood sugar, Qtrilmet may not be recommended to use;
- if you take any of the following medicines: glucocorticoids, beta-2 agonists, diuretics, carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin as they may reduce the effect of Qtrilmet (see "Other medicines and Qtrilmet");
- if you are 75 years old or older;
- if blood tests show that the amount of red blood cells in your blood is too high.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before taking Qtrilmet.

Surgery and operations
If you need major surgery, you must stop taking Qtrilmet during and for some time after the operation. Your doctor will decide when to stop and when to restart your treatment with Qtrilmet.

Diabetic skin and foot problems
Skin damage, such as sores or ulcers is a common complication of diabetes. Rash can occur with both saxagliptin and dapagliflozin (see section 4). Follow the recommendations for skin care from your doctor or nurse. Contact your doctor if you encounter blistering of the skin, as it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Qtrilmet.

It is important to check your feet regularly – and follow the advice on foot care from your health care professional.

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

Kidney function
You should have a blood test to check how well your kidneys are working before you start taking and while you are on this medicine. Your kidney function will be checked at least once every year or more frequently if you are elderly or if you have worsening kidney function.

Urine test
Because of how Qtrilmet works, your urine will test positive for sugar while you are on this medicine.

Children and adolescents
Qtrilmet is not recommended for children and adolescents under 18 years of age because it has not been studied in these patients.

Other medicines and Qtrilmet
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. In particular, talk to your doctor before taking Qtrilmet if you are taking any of the following medicines:

- medicines to lower blood pressure including ACE inhibitors (such as enalapril or ramipril), angiotensin II receptor antagonists (such as losartan or candesartan);
- insulin, sulphonylureas (such as glimepiride) or pioglitazone to lower your blood sugar;
- medicines that increase urine production and lower blood pressure (diuretics). Your doctor may ask you to stop taking Qtrilmet. Possible signs of losing too much fluid from your body are listed in section 4;
- medicines that may change the amount of metformin in your blood, especially if you have reduced kidney function (such as verapamil, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib or olaparib);
- if you are using medicines containing any of the following active substances:
    - beta-2 agonists – used to treat asthma,
    - carbamazepine, phenobarbital or phenytoin – medicines for preventing fits (seizure) or some types of long-term pain,
    - cimetidine – used to treat stomach problems,
    - corticosteroids such as dexamethasone – used to treat inflammation in diseases like asthma and arthritis,
    - diltiazem – used to treat angina (chest pain) and lower blood pressure,
    - ketoconazole tablets – used to treat Cushing's syndrome (when the body produces an excess of cortisol),
    - rifampicin – an antibiotic used to treat infections such as tuberculosis,
    - non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and celecoxib (a 'COX-2-inhibitor') – used to treat pain and inflammation.

If any of the above apply to you (or if you are not sure), talk to your doctor before taking Qtrilmet.

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Qtrilmet before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Qtrilmet.

Qtrilmet with alcohol
Avoid excessive alcohol intake while taking Qtrilmet since this may increase the risk of lactic acidosis (see "Warnings and precautions" and "Do not take Qtrilmet if you").

Pregnancy and breast-feeding
Qtrilmet is not recommended during pregnancy and your doctor will ask you to stop taking this medicine if you become pregnant or plan to have a baby. Talk to your doctor about the best way to control your blood sugar while you are pregnant.

You should not use Qtrilmet if you are breast-feeding or plan to breast-feed. Metformin passes into breast milk in small amounts. It is not known if saxagliptin and dapagliflozin pass into breast milk. Talk to your doctor before taking this medicine if you would like to breast-feed or you are breast-feeding your baby.

Driving and using machines
Qtrilmet is not expected to affect you being able to drive a car or use any tools or machines. However, if you feel dizzy while taking Qtrilmet, do not drive or use tools or machines. Also, it may be dangerous to drive or use machines if your blood sugar levels fall too low (hypoglycaemia), which can cause shaking, sweating, fast heartbeat, change in vision, headache and confusion.

Qtrilmet contains lactose

Qtrilmet contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take Qtrilmet

Always take this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Your doctor will prescribe an appropriate dose of Qtrilmet depending on your blood sugar level and the diabetes medicines you were taking before. The recommended dose is two tablets once a day.

The maximum recommended daily dose of Qtrilmet is metformin 2,000 mg, saxagliptin 5 mg and dapagliflozin 10 mg.

Switching to Qtrilmet
If you are already taking metformin, saxagliptin and dapagliflozin as single tablets or saxagliptin and dapagliflozin as a combination together with metformin, your doctor may ask you to switch to this medicine so you only need to take one tablet. To avoid overdose, do not continue taking the separate tablets of these medicines as well as Qtrilmet.

Taking this medicine
- Swallow the tablets whole with half a glass of water.
- Take your tablets with food. This is to reduce the risk of side effects on the stomach.
- Take the tablets at around the same time each day.

You may see some remains of the tablet shell in your stools. This is normal and what is left of the tablet after all the medicine has been released.

Your doctor may prescribe other medicines to lower the amount of sugar in your blood. Remember to take other medicines as your doctor has told you. This will help get the best results for your health.

Diet and exercise
To control your diabetes, you need to follow your doctor's advice on diet and exercise, even when you are taking this medicine. In particular, if you are following a diabetic weight control diet, continue to follow it while you are taking Qtrilmet.

If you take more Qtrilmet than you should
If you take more Qtrilmet tablets than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you. High overdose may lead to lactic acidosis (see sections 2 and 4).

If you forget to take Qtrilmet
What to do if you forget to take Qtrilmet on time.
- If it is less than 12 hours since you should have taken your daily dose, take a dose of Qtrilmet as soon as you remember. Then take your next dose at the usual time.
- If it is more than 12 hours since you should have taken your daily dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose of Qtrilmet to make up for a forgotten dose.

If you stop taking Qtrilmet
Do not stop taking Qtrilmet without talking to your doctor first. Your blood sugar may rise without this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some symptoms need immediate medical attention:
Stop taking Qtrilmet and see a doctor straight away if you notice any of the following serious side effects:

- **Serious allergic (hypersensitivity) reaction,** seen rarely (may affect up to 1 in 1,000 people)
  Symptoms of serious allergic reaction:
  - rash,
  - raised red patches on your skin (hives),
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

  Your doctor may prescribe a medicine to treat your allergic reaction and change your diabetes medicine.

- **Lactic acidosis,** seen very rarely (may affect up to 1 in 10,000 people)
  Qtrilmet may cause a very rare, but very serious side effect called lactic acidosis.
  Symptoms of lactic acidosis include:
  - vomiting,
  - stomach ache (abdominal pain),
  - muscle cramps,
  - general feeling of not being well with severe tiredness,
  - difficulty in breathing,
  - reduced body temperature and slower heartbeat.

  If this happens you must **stop taking Qtrilmet and contact a doctor or the nearest hospital immediately,** as lactic acidosis may lead to coma.

- **Pancreatitis**, seen uncommonly (may affect up to 1 in 100 people)
  Signs of pancreatitis:
  - severe and persistent pain in the abdomen (stomach area) which might reach through to your back,
  - nausea and vomiting.

- **Dehydration (loss of too much fluid from your body)**, seen uncommonly (may affect up to 1 in 100 people)
  Signs of dehydration:
  - very dry or sticky mouth, feeling very thirsty,
  - feeling very sleepy or tired,
  - passing little or no water (urine),
  - fast heartbeat.

- **Urinary tract infection**, seen commonly (may affect up to 1 in 10 people)
  Signs of a severe infection of the urinary tract include:
  - fever, chills,
  - burning sensation when passing water (urinating),
  - altered urinary frequency, including urgent need to urinate more often,
  - smelly or cloudy appearance of urine,
  - pain in your back or side.

- **Diabetic ketoacidosis**, seen rarely (may affect up to 1 in 1,000 people)
  Signs of diabetic ketoacidosis (see also section 2 “Warnings and precautions”):

- increased levels of "ketone bodies" seen in your urine or blood tests,
- rapid weight loss,
- feeling sick or being sick,
- stomach pain,
- excessive thirst,
- fast and deep breathing,
- confusion,
- unusual sleepiness or tiredness,
- a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat.

This may occur regardless of blood glucose level. Your doctor may decide to temporarily or permanently stop your treatment with Qtrilmet.

Stop taking Qtrilmet and see a doctor straight away, if you notice any of the serious side effects above.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

- **Necrotising fasciitis of the perineum** or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely (see section 2 "Diabetic skin and foot problems").

Contact your doctor as soon as possible if you have any of the following side effects:

- **Low blood sugar levels (hypoglycaemia)**, seen very commonly (may affect more than 1 in 10 people) if used with other diabetes medicines which cause hypoglycaemia.
  Signs of low blood sugar:
  - shaking, sweating, feeling very anxious, fast heartbeat,
  - feeling hungry, headache, change in vision,
  - a change in your mood or feeling confused.

  Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above.

Other side effects when taking Qtrilmet include:
Very common
- nausea, vomiting
- diarrhoea or stomach ache
- loss of appetite
- upper respiratory tract infection including:
  - infection of the upper chest or lungs,
  - infection of the sinuses with a feeling of pain and fullness behind your cheeks and eyes (sinusitis),
  - inflamed nose or throat (nasopharyngitis) (signs of this may include a cold or a sore throat).

Common
- genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- back pain
- passing more water (urine) than usual or needing to pass water more often
- dizziness
- tiredness
- severe joint pain (arthralgia)
- stomach ache and indigestion (dyspepsia)
- vomiting, inflammation of the stomach (gastritis)
- inflamed stomach or gut usually caused by an infection (gastroenteritis)

- headache, muscle pain (myalgia)
- changes in blood tests (changes in the amount of cholesterol or fats in your blood, increases in the amount of red blood cells in your blood or decreases in creatinine renal clearance)
- rash
- changes in taste
- swelling of the hands, ankles or feet (peripheral oedema)

Uncommon
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth
- weight decrease
- decrease in kidney function, increases in creatinine or urea (shown in blood tests)
- skin rash that may include raised bumps, skin irritation, or itchiness
- difficulties in getting or maintaining an erection (erectile dysfunction)
- fungal infection
- mild allergic (hypersensitivity) reaction (rash)
- itching in the genital area (genital pruritus or vulvovaginal pruritus) or discomfort while urinating

Very rare
- decreased vitamin B_{12} levels in the blood
- abnormalities in liver function tests, inflammation of the liver (hepatitis)
- redness of the skin (erythema), itching, or an itchy rash (hives)

Not known (frequency cannot be estimated from the available data)
- blistering of the skin (bullous pemphigoid)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Qtrilmet

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and carton after 'EXP'. The expiry date refers to the last day of that month.

PVC/PCTFE/alu blister:
Do not store above 30°C.

PA/alu/PVC/alu blister:
This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Qtrilmet contains
- The active substances are metformin, saxagliptin and dapagliflozin.

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets:
- Each tablet contains 850 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets:
- Each tablet contains 1,000 mg of metformin hydrochloride, saxagliptin hydrochloride equivalent to 2.5 mg saxagliptin and dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

- The other ingredients are:
  - tablet core: carmellose sodium (E466) (see section 2 'Sodium content'); cellulose, microcrystalline (E460i); crospovidone (E1202); hypromellose (E464); lactose (see section 2 'Qtrilmet contains lactose'); magnesium stearate (E470b); silica, dental type (E551).
  - film-coating:
    Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets:
    Macrogol (E1521); poly(vinyl alcohol) (E1203); titanium dioxide (E171); talc (E553b); yellow iron oxide (E172); red iron oxide (E172); black iron oxide (E172).
    Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets:
    Macrogol (E1521); poly(vinyl alcohol) (E1203); titanium dioxide (E171); talc (E553b); yellow iron oxide (E172); black iron oxide (E172).

What Qtrilmet looks like and contents of the pack
Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets are beige, biconvex, 11 x 21 mm oval tablet, with 3005 debossed on one side.

Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets are green, biconvex, 11 x 21 mm oval tablet, with 3002 debossed on one side.

Qtrilmet 850 mg/2.5 mg/5 mg modified-release tablets and Qtrilmet 1,000 mg/2.5 mg/5 mg modified-release tablets are available in blister. The pack sizes are 14, 28, 56 and 196 modified-release tablets in calendar blisters and 14, 28, 56, 60 and 196 modified-release tablets in blisters.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu