▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – SEGLUROMET®
(Ertugliflozin/Metformin)

1 NAME OF THE MEDICINE

Ertugliflozin /metformin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SEGLUROMET contains ertugliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

SEGLUROMET is available for oral use as film-coated tablets containing:

- 3.24 mg ertugliflozin pyroglutamic acid equivalent to 2.5 mg of ertugliflozin and 500 mg metformin hydrochloride (SEGLUROMET 2.5/500)
- 3.24 mg ertugliflozin pyroglutamic acid equivalent to 2.5 mg of ertugliflozin and 1000 mg metformin hydrochloride (SEGLUROMET 2.5/1000)
- 9.71 mg ertugliflozin pyroglutamic acid equivalent to 7.5 mg of ertugliflozin and 500 mg metformin hydrochloride (SEGLUROMET 7.5/500)
- 9.71 mg ertugliflozin pyroglutamic acid equivalent to 7.5 mg of ertugliflozin and 1000 mg metformin hydrochloride (SEGLUROMET 7.5/1000)

For the full list of excipients see Section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

SEGLUROMET, 2.5 / 500 pink, oval, film-coated tablets debossed with “2.5/500” on one side and plain on the other side.

SEGLUROMET 2.5 / 1000 pink, oval, film-coated tablets debossed with “2.5/1000” on one side and plain on the other side.

SEGLUROMET 7.5 / 500 red, oval, film-coated tablets debossed with “7.5/500” on one side and plain on the other side.

SEGLUROMET 7.5 / 1000 red, oval, film-coated tablets debossed with “7.5/1000” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SEGLUROMET (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate

[see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and 4.2 DOSE AND METHOD OF ADMINISTRATION].

4.2 DOSE AND METHOD OF ADMINISTRATION

General

- Take SEGLUROMET twice daily with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin.
- Individualise the starting dose of SEGLUROMET (ertugliflozin and metformin hydrochloride) based on the patient's current regimen:
    - In patients on metformin, switch to SEGLUROMET tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin.
    - In patients already treated with ertugliflozin and metformin, switch to SEGLUROMET tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and 2,000 mg metformin HCl.

Renal impairment

Assess renal function prior to initiation of SEGLUROMET and periodically thereafter [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

SEGLUROMET is contraindicated in patients with an eGFR less than 60 mL/min/1.73 m^2 [see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Hepatic impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. SEGLUROMET is not recommended in patients with hepatic impairment [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Elderly

No dosage adjustment of SEGLUROMET is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and metformin is known to be substantially excreted by the kidneys, care should be taken in dose selection in the elderly. It may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Paediatric population

Safety and effectiveness of SEGLUROMET in paediatric patients under 18 years of age have not been established.

4.3 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to SEGLUROMET, ertugliflozin, metformin hydrochloride, or to any of the excipients.
- Moderate or severe renal impairment (eGFR less than 60 mL/min/1.73 m^2) [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, or intravascular administration of iodinated contrast agents [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, pulmonary embolism, recent myocardial infarction, shock, acute significant blood loss, sepsis, gangrene, pancreatitis.
- During or immediately following surgery where insulin is essential.
- Due to its metformin component, SEGLUROMET is contraindicated in patients with conditions that can lead to severe hepatic insufficiency such as:
    - acute alcohol intoxication
    - alcoholism

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

SEGLUROMET should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Lactic acidosis

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

There have been post-marketing cases of lactic acidosis in patients receiving metformin, a component of SEGLUROMET, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap

acidosis (without evidence of ketonuria or ketonaemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of SEGLUROMET. In SEGLUROMET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good haemodynamic conditions). Haemodialysis has often resulted in reversal of symptoms and recovery.

Information on the known and possible risk factors for metformin-associated lactic acidosis is provided below:

Renal impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in patients with renal impairment].

Drug interactions: The concomitant use of SEGLUROMET with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant haemodynamic change, interfere with acid base balance, or increase metformin accumulation (e.g., cationic drugs) [see 4.5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS]. Therefore, consider more frequent monitoring of patients.

Age 65 or greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Radiological studies with contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop SEGLUROMET at the time of, or prior to, an iodinated contrast imaging. Re-evaluate eGFR 48 hours after the imaging procedure, and restart SEGLUROMET if renal function is stable.

Surgery: see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Surgery.

Hypoxic states: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotaemia. When such events occur, discontinue SEGLUROMET.

Excessive alcohol intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving SEGLUROMET [see 4.3 CONTRAINDICATIONS].

Hepatic impairment: Patients with hepatic impairment have developed metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. SEGLUROMET is not recommended in patients with hepatic impairment.

Hypotension

Ertugliflozin, a component of SEGLUROMET, causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating SEGLUROMET [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)] particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients (≥ 65 years), or patients on diuretics. Before initiating SEGLUROMET, intravascular volume status should be assessed and patients advised on the importance of adequate hydration. Monitor intravascular volume status in addition to blood pressure and renal function after initiating therapy.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness, heat stress or severe infections), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving SEGLUROMET. Temporary interruption of SEGLUROMET should be considered until the fluid loss is corrected.

Ketoacidosis

SEGLUROMET should not be used for the treatment of diabetic ketoacidosis.

Reports of ketoacidosis, including diabetic ketoacidosis, a serious life-threatening condition requiring urgent hospitalisation, have been identified in clinical trials and postmarketing surveillance in patients receiving sodium glucose co-transporter-2 (SGLT2) inhibitors. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. SEGLUROMET is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with SEGLUROMET who present with signs and symptoms consistent with severe metabolic acidosis should be promptly assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with SGLT2 inhibitors may be present even if blood glucose levels are less than 14 mmol/L. If ketoacidosis is suspected, SEGLUROMET should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement. Signs and symptoms of ketoacidosis may include excessive thirst, nausea, vomiting, abdominal pain, generalised malaise, and shortness of breath.

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

Before initiating SEGLUROMET, consider factors in the patient history that may predispose to ketoacidosis.

Factors that predispose patients to ketoacidosis include a low carbohydrate diet, dehydration, acute illness, surgery [see Surgery below], a previous ketoacidosis, insulin dose reduction, malnourishment / reduced caloric intake or increased insulin requirements due to infections, insulin deficiency from any cause (including insulin pump failure, or history of pancreatitis or pancreatic surgery), and alcohol abuse. SEGLUROMET should be used with caution in these patients. Consider monitoring for ketoacidosis and temporarily discontinuing SEGLUROMET in clinical situations known to predispose to ketoacidosis.

Surgery

Treatment with SEGLUROMET must be discontinued at least 48 hours prior to major surgery [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Ketoacidosis and Lactic acidosis]. An increase in other glucose lowering agents may be required during this time.

Patients scheduled for non-urgent surgery who have not ceased SEGLUROMET should be assessed and consideration should be given to postponing the procedure.

Therapy may be restarted not earlier than 48 hours following surgery, once the patient's condition has stabilised, oral intake is normal, and only if normal renal function has been established, as withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment.

Hypoglycaemia with concomitant use with insulin and insulin secretagogues

Ertugliflozin
Insulin and insulin secretagogues are known to cause hypoglycaemia. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycaemia when used in combination with SEGLUROMET.

Metformin
Hypoglycaemia does not occur in patients receiving metformin, alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people who are taking β-adrenergic blocking drugs.

Genital mycotic infections

Ertugliflozin, a component of SEGLUROMET, increases the risk of genital mycotic infections. In trials with SGLT2 inhibitors, patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Monitor and treat appropriately.

Necrotising Fasciitis of the Perineum

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors. Serious outcomes have included hospitalisation, multiple surgeries, and death.

Patients treated with SEGLUROMET who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, and malaise should be evaluated for necrotising fasciitis. If suspected, SEGLUROMET should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Caution is advised in patients at increased risk of genital infections including patients with recurrent or pre-existing urogenital infections, obesity, immunosuppressed states, smoking, alcohol abuse, end-stage renal or liver failure, and HbA1c >10%.

Vitamin B_{12} levels

In controlled clinical trials of metformin, a component of SEGLUROMET, of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12} intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on SEGLUROMET and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Use in patients with renal impairment

SEGLUROMET
SEGLUROMET is not recommended in patients with moderate and severe renal impairment [see 4.3 CONTRAINDICATIONS].

Monitoring of renal function is recommended:

- prior to initiating SEGLUROMET and periodically thereafter, i.e. at least yearly;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- more frequently (2 to 4 times per year) in patients approaching moderate renal impairment (eGFR of 60 mL/min/1.73 m^2) or those at increased risk for the development of renal impairment (e.g., the elderly).

SEGLUROMET should be discontinued when eGFR is persistently below 60 mL/min/1.73m^2 or CrCl is persistently below 60 mL/min [see 4.3 CONTRAINDICATIONS].

Ertugliflozin
The efficacy of ertugliflozin is dependent on renal function. Ertugliflozin increases serum creatinine and decreases eGFR; patients with moderate renal impairment at baseline have larger mean changes [see 4.8 ADVERSE REACTIONS (UNDESIRABLE EFFECTS) and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

The efficacy and safety of ertugliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Ertugliflozin is not expected to be effective in these patient populations.

Metformin hydrochloride
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Urosepsis and pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Discontinuation of SEGLUROMET may be considered in cases of recurrent urinary tract infections.

Use in the elderly

Elderly patients may be at an increased risk of volume depletion. Patients 65 years and older treated with ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared to younger patients. The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. SEGLUROMET is expected to have diminished efficacy in elderly patients with renal impairment [see 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Assess renal function more frequently in elderly patients.

Paediatric use

Safety and effectiveness of SEGLUROMET in paediatric patients under 18 years of age have not been established.

Lower limb amputations

A numerical imbalance in non-traumatic lower limb amputations (primarily of the toe) was observed in patients treated with ertugliflozin across 7 Phase 3 clinical trials in the ertugliflozin development program. In these trials, 11 patients in the ertugliflozin group (0.3%) and 1 patient in the comparator group (0.1%) reported lower limb amputations. A causal association between ertugliflozin and lower limb amputation has not been definitively established.

An increase in cases of lower limb amputation (primarily of the toe) has also been observed in clinical trials with another SGLT2 inhibitor. It is important to counsel patients on routine preventative foot-care.

Effects on laboratory tests

Ertugliflozin

Positive urine glucose test
Monitoring glycaemic control with urine glucose tests is not recommended in patients taking medicines containing an SGLT2 inhibitor as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycaemic control.

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 medicines containing an SGLT2 inhibitor. Use alternative methods to monitor glycaemic control.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

SEGLUROMET
No clinically significant pharmacokinetic interaction was seen when ertugliflozin was coadministered with metformin.

Pharmacokinetic drug interaction studies with SEGLUROMET have not been performed; however, such studies have been conducted with ertugliflozin and metformin, the individual components of SEGLUROMET.

***In vitro* assessment of drug interactions with ertugliflozin**

In *in vitro* studies, ertugliflozin and its two major glucuronide metabolites did not inhibit CYP450 isoenzymes (CYPs) 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4 at clinically relevant concentrations, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin was not a time-dependent inhibitor of CYP3A *in vitro*. As well ertugliflozin and its two major glucuronide metabolites did not inhibit UGT1A1, 1A4, 1A6, 1A9, or 2B7 *in vitro* at clinically relevant concentrations. Only weak inhibitory activity was observed, with the IC_{50} at the most sensitive target (39 μM for ertugliflozin against UGT1A4) almost 1000 times higher than the peak plasma concentration of unbound drug in patients at the MRHD of 15 mg/day. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of drugs eliminated by these enzymes. Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3, OATP2B1). Ertugliflozin or its two major glucuronide metabolites do not meaningfully inhibit P-gp, BCRP, OCT1, OCT2, OAT1, OAT3 transporters, or transporting polypeptides OATP1B1 or OATPB3 *in vitro* at clinically relevant concentrations. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

***In vivo* assessment of drug interactions with ertugliflozin**

No dose adjustment of SEGLUROMET is recommended when coadministered with commonly prescribed medicinal products. Ertugliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, sitagliptin, and simvastatin in healthy subjects (see Figure 1). Coadministration of ertugliflozin with multiple doses of 600 mg once daily rifampicin (an inducer of UGT and CYP enzymes) resulted in approximately 39% and 15% mean reductions in ertugliflozin AUC and C_{max}, respectively, relative to ertugliflozin administered alone. These changes in exposure are not considered clinically relevant. Ertugliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, sitagliptin, and simvastatin when coadministered in healthy subjects (see Figure 2). Physiologically-based PK (PBPK) modelling suggests that coadministration of mefenamic acid (UGT inhibitor) may increase the AUC and C_{max} of ertugliflozin by 1.51- and 1.19-fold, respectively. These predicted changes in exposure are not considered clinically relevant.

Clinical studies of the effects of other drugs on the pharmacokinetics of ertugliflozin (see Figure 1)

The effects of coadministered drugs on the pharmacokinetics of ertugliflozin have been assessed in drug-drug interaction studies. There were no clinically significant drug interactions identified.

Sitagliptin
Single-dose administration of sitagliptin 100 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The geometric mean ratios (GMR) and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with sitagliptin vs. ertugliflozin alone were 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively.

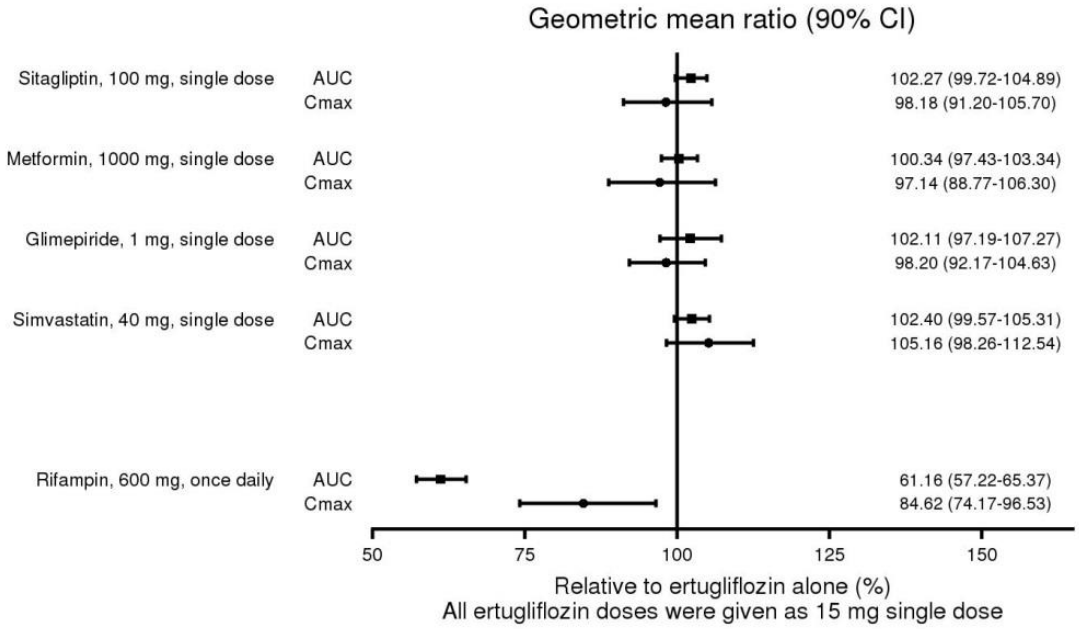
Metformin
Single-dose administration of metformin 1,000 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with metformin vs. ertugliflozin alone were 100.34% (97.43%, 103.34%) and 97.14 % (88.77%, 106.30%), respectively.

Glimepiride
Single-dose administration of glimepiride 1 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with glimepiride vs. ertugliflozin alone were 102.11% (97.19%, 107.27%) and 98.20% (92.17%, 104.63%), respectively.

Simvastatin
Single-dose administration of simvastatin 40 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with simvastatin vs. ertugliflozin alone were 102.40% (99.57%, 105.31%) and 105.16% (98.26%, 112.54%), respectively.

Rifampicin
Multiple-dose administration of rifampicin 600 mg q.d.x 10 days was associated with a decrease in exposure of ertugliflozin 15 mg. The GMR and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with rifampicin vs. ertugliflozin alone were 61.16% (57.22%, 65.37%) and 84.62% (74.17%, 96.53%), respectively.

Figure 1 Effects of Other Drugs on the Pharmacokinetics of Ertugliflozin



Clinical studies of the effects of ertugliflozin on the pharmacokinetics of other drugs (see Figure 2)

The effects of ertugliflozin on the pharmacokinetics of coadministered drugs have been assessed in drug-drug interaction studies. There were no clinically significant drug interactions identified.

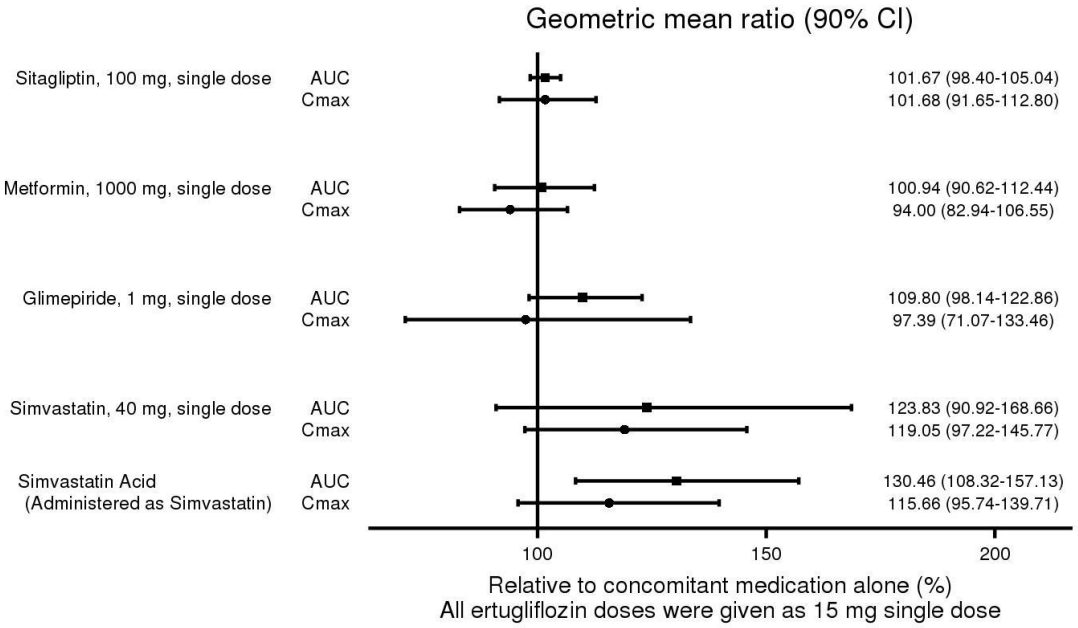
Sitagliptin
No clinically meaningful change in sitagliptin exposure was observed following concomitant administration of a single 100 mg sitagliptin dose with 15 mg ertugliflozin compared to sitagliptin alone. The GMR and 90% CI (expressed as percentages) for sitagliptin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. sitagliptin alone were 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively.

Metformin
No clinically meaningful change in metformin exposure was observed following concomitant administration of a single 1,000 mg metformin dose with 15 mg ertugliflozin compared to metformin alone. The GMR and 90% CI (expressed as percentages) for metformin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. metformin alone were 100.94% (90.62%, 112.44%) and 94.00% (82.94%, 106.55%), respectively.

Glimepiride
No clinically meaningful change in glimepiride exposure was observed following concomitant administration of a single 1 mg glimepiride dose with 15 mg ertugliflozin compared to glimepiride alone. The GMR and 90% CI (expressed as percentages) for glimepiride AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. glimepiride alone were 109.80% (98.14%, 122.86%) and 97.39% (71.07%, 133.46%), respectively.

Simvastatin
Coadministration of a single 40 mg simvastatin dose with a single dose of ertugliflozin 15 mg resulted in a small, non-clinically meaningful increase in AUC_{inf} and C_{max} of simvastatin and simvastatin acid. The GMR and 90% CI (expressed as percentages) for simvastatin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. simvastatin alone were 123.83% (90.92%, 168.66%) and 119.05% (97.22%, 145.77%), respectively. The GMR and 90% CI for simvastatin acid AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. simvastatin alone were 130.46% (108.32%, 157.13%) and 115.66% (95.74%, 139.71%), respectively.

Figure 2 Effects of Ertugliflozin on the Pharmacokinetics of Other Drugs



Drug interactions with metformin hydrochloride

Drugs that increase the risk of lactic acidosis

- *Carbonic Anhydrase Inhibitors*

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloraemic metabolic acidosis. Concomitant use of these drugs with SEGLUROMET may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

- *Loop diuretics:* May increase the risk of lactic acidosis due to their potential to decrease renal function.

Drugs that reduce metformin clearance
Drugs that are eliminated by renal tubular secretion have the potential for interaction with metformin by competing for common renal tubular transport systems, and may increase the accumulation of metformin and the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Cationic drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple dose metformin cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of SEGLUROMET, and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Alcohol
The risk of lactic acidosis increases with acute intoxication, particularly in cases of fasting or malnutrition and hepatic insufficiency. Alcohol may make the signs of hypoglycaemia less clear, and delayed hypoglycaemia can occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving and operation of dangerous machinery much more hazardous.

Drugs that affect glycaemic control

Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving SEGLUROMET, the patient should be closely observed to maintain adequate glycaemic control.

Glyburide
In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide area under the curve (AUC) and peak concentration (C_{max}) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide
A single-dose, metformin furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any

significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine
A single-dose, metformin nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Beta-Blockers
Co-administration of metformin and beta-blockers may result in a potentiation of the anti-hyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

Other
In healthy volunteers, the pharmacokinetics of metformin and ibuprofen were not affected when coadministered in single dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of SEGLUROMET or its individual components on fertility in humans has not been studied. No animal fertility studies have been performed with ertugliflozin and metformin in combination.

Ertugliflozin
In rats, no effects on male or female fertility were observed with oral administration of ertugliflozin up to the highest dose of 250 mg/kg/day (yielding approximately 280 and 380 times the clinical plasma AUC for unbound ertugliflozin at the maximum recommended human dose (MRHD) of 15 mg/day in the respective sexes).

Metformin hydrochloride
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Use in pregnancy (Category D)

SEGLUROMET
There are no adequate and well-controlled studies of SEGLUROMET or its individual components in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation. No animal embryofetal development studies have been performed with ertugliflozin and metformin in combination. Use of SEGLUROMET during pregnancy is not recommended.

Ertugliflozin
In animal studies, ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at oral doses up to 100 mg/kg/day and 250 mg/kg/day in the respective species (yielding approximately 240 and >1000 times the clinical AUC for unbound ertugliflozin at the MRHD of 15 mg/day). At a maternally toxic dose in rats (250 mg/kg/day), lower fetal viability and a higher incidence of cardiac malformation were observed (510 times the clinical exposure at the MRHD, based on AUC). Ertugliflozin and/or its metabolites were shown to cross the placenta in rats.

The developing kidney is seen to be more sensitive to ertugliflozin than the mature organ. When ertugliflozin was administered to juvenile rats from postnatal day (PND) 21 to PND 90, increased kidney weights, dilatation of the renal pelvis and tubules, and renal mineralization were seen at all dose levels tested (≥5 mg/kg/day, yielding 13 times the clinical exposure at the MRHD) with effects more prominent than observed in adult animals.

Metformin hydrochloride
Metformin did not adversely affect developmental outcomes when administered to rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 3 and 6 times the maximum recommended human dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Use in lactation

There is no information regarding the presence of ertugliflozin in human milk, the effects on the breast-fed infant, or the effects on milk production. Metformin is present in human breast milk. Ertugliflozin was shown to be excreted in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney, based on data with ertugliflozin (see Use in pregnancy).

Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants SEGLUROMET is not recommended during breast-feeding.

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

SEGLUROMET has no or negligible influence on the ability to drive or use machines. Patients should be alerted to the risk of hypoglycaemia when SEGLUROMET is used in combination with insulin or an insulin secretagogue and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Ertugliflozin and Metformin
The safety of concomitantly administered ertugliflozin and metformin has been evaluated in 1,083 patients with type 2 diabetes mellitus for 26 weeks in a pool of two placebo-controlled trials: as ertugliflozin add-on therapy to metformin and as ertugliflozin add-on therapy to sitagliptin and metformin [see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials]. The incidence and type of adverse reactions in these two trials were similar to the adverse reactions seen with ertugliflozin. There were no additional adverse reactions identified in the pooling of the two placebo-controlled trials that included metformin relative to the three placebo-controlled studies with ertugliflozin (see below).

Ertugliflozin

Pool of placebo-controlled trials evaluating ertugliflozin 5 and 15 mg
The primary assessment of safety and tolerability was conducted in a pooled analysis of three 26-week placebo-controlled trials with similar study design, duration of treatment, and baseline characteristics. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials [see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials]. These data reflect exposure of 1,029 patients to ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg (N=510), or placebo (N=515) once daily. The data in Table 1 are derived from this pooled analysis.

The overall incidence of subjects with 1 or more adverse events was not notably different across the ertugliflozin 5 mg (45.5%), ertugliflozin 15 mg (50.4%), and placebo (51.1%) groups. The incidence of non-fatal serious adverse events was low and similar in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (3.3%, 2.4%, and 2.9% for the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups, respectively). The incidence of adverse events resulting in discontinuation from study medication was low overall and not notably different in the ertugliflozin 5 mg and 15 mg groups (2.3% and 1.4%, respectively) relative to the placebo groups (1.7%).

The adverse drug reactions (ADRs) listed in Table 1 are presented by System Organ Class (SOC).

Table 1. Adverse Drug Reactions Reported in Patients Receiving Ertugliflozin

Body System/Organ Class Adverse Reaction	Ertugliflozin 5 mg %	Ertugliflozin 15 mg %	Placebo %
	N = 519	N = 510	N = 515
Infections and infestations			
Female genital mycotic infections*	9.1	12.2	3.0
Male genital mycotic infections†	3.7	4.2	0.4
Renal and urinary disorders			
Increased urination‡	2.7	2.4	1.0
Reproductive system and breast disorders			
Vulvovaginal pruritus	1.0	1.2	0.2
General disorders and administration site conditions			
Thirst§	1.3	1.0	0.2

* Includes: genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. Percentages calculated with the number of female patients in each group as denominator: placebo (N=235), ertugliflozin 5 mg (N=252), ertugliflozin 15 mg (N=245).

† Includes: balanitis candida, balanoposthitis, genital infection, and genital infection fungal. Percentages calculated with the number of male patients in each group as denominator: placebo (N=280), ertugliflozin 5 mg (N=267), ertugliflozin 15 mg (N=265).

‡ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.

§ Includes: thirst and polydipsia.

Description of selected adverse reactions

Volume depletion

Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2). In the pool of three placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension) were not more frequent in patients treated with ertugliflozin compared to those treated with placebo; events were reported by 0.8%, 1.0%, and 1.7% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. A higher incidence was seen in a study of patients with moderate renal impairment; events were reported by 4.4%, 1.9%, and 0% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Ertugliflozin may also increase the risk of hypotension in other patients at risk for volume contraction [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Ketoacidosis

Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Impairment in renal function

Use of ertugliflozin was associated with increases in serum creatinine and decreases in eGFR [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on laboratory tests]. Patients with moderate renal impairment at baseline had larger mean changes; these changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes may play a role in the renal function abnormalities observed with

ertugliflozin [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 2.5%, 1.3%, and 0.6% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively.

Hypoglycaemia

In all clinical trials, hypoglycaemia was defined as any event regardless of symptoms, where biochemical hypoglycaemia was documented (any glucose value below or equal to 3.9 mmol/L). Severe hypoglycaemia was defined as an event consistent with hypoglycaemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained).

The incidence of hypoglycaemia by study is shown in Table 2. The incidence of hypoglycaemia may be higher when ertugliflozin is administered with insulin and/or an insulin secretagogue [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Table 2. Incidence of Overall* and Severe† Hypoglycaemia in Placebo- or Comparator-Controlled Clinical Studies

Monotherapy (26 weeks)	**Ertugliflozin 5 mg (N =156)**	**Ertugliflozin 15 mg (N = 152)**	**Placebo (N = 153)**		
Overall [N (%)]	4 (2.6)	4 (2.6)	1 (0.7)		
Severe [N (%)]	0 (0.0)	2 (1.3)	0 (0.0)		
Add-on Combination Therapy with Metformin (26 weeks)	**Ertugliflozin 5 mg (N = 207)**	**Ertugliflozin 15 mg (N = 205)**	**Placebo (N = 209)**		
Overall [N (%)]	15 (7.2)	16 (7.8)	9 (4.3)		
Severe [N (%)]	1 (0.5)	0 (0.0)	1 (0.5)		
Active-Controlled Study with Glimepiride as Add-on Combination Therapy with Metformin (52 weeks)	**Ertugliflozin 5 mg (N = 448)**	**Ertugliflozin 15 mg (N = 440)**	**Glimepiride (N = 437)**		
Overall [N (%)]	25 (5.6)	36 (8.2)	119 (27.2)		
Severe [N (%)]	1 (0.2)	1 (0.2)	10 (2.3)		
Factorial Study with Sitagliptin as Add-on Combination Therapy with Metformin (26 weeks)	**Ertugliflozin 5 mg (N = 250)**	**Ertugliflozin 15 mg (N = 248)**	**Sitagliptin (N = 247)**	**Ertugliflozin 5 mg + Sitagliptin (N = 243)**	**Ertugliflozin 15 mg + Sitagliptin (N = 244)**
Overall [N (%)]	14 (5.6)	13 (5.2)	9 (3.6)	13 (5.3)	22 (9.0)
Severe [N (%)]	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Add-on Combination Therapy with Metformin and Sitagliptin (26 weeks)	**Ertugliflozin 5 mg (N = 156)**	**Ertugliflozin 15 mg (N = 153)**	**Placebo (N = 153)**		
Overall [N (%)]	7 (4.5)	3 (2.0)	5 (3.3)		
Severe [N (%)]	1 (0.6)	0 (0.0)	1 (0.7)		
Initial Combination Therapy with Sitagliptin (26 weeks)			**Placebo (N = 97)**	**Ertugliflozin 5 mg + Sitagliptin (N = 98)**	**Ertugliflozin 15 mg + Sitagliptin (N = 96)**
Overall [N (%)]			1 (1.0)	6 (6.1)	3 (3.1)
Severe [N (%)]			0 (0.0)	0 (0.0)	2 (2.1)
In Combination with Insulin and/or an Insulin Secretagogue in Patients with Moderate Renal Impairment (26 weeks)	**Ertugliflozin 5 mg (N = 148)**	**Ertugliflozin 15 mg (N = 143)**	**Placebo (N = 133)**		
Overall [N (%)]	53 (35.8)	39 (27.3)	48 (36.1)		
Severe [N (%)]	5 (3.4)	3 (2.1)	3 (2.3)		

* Overall hypoglycaemic events: plasma or capillary glucose of less than or equal to 3.9 mmol/L.

† Severe hypoglycaemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

Genital mycotic infections
In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12.2%, and 3.0% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively. [See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.]

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively. In rare instances, phimosis was reported and sometimes circumcision was performed. [See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

Metformin
Metformin adverse reactions are shown below by system organ class and by frequency category. Frequency categories are based on information available from the Product Information for metformin available in Australia. Frequencies are defined as follows: very common: >1/10; common >1/100, <1/10; uncommon >1/1,000, <1/100; rare >1/10,000, <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders: *Common:* Taste disturbance.

Gastrointestinal disorders: *Very common:* Gastrointestinal disorders such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders: *Very rare:* Skin reactions such as erythema, pruritus and urticaria.

Metabolism and nutrition disorders: *Very rare:*

- Lactic acidosis [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].
- Decrease of vitamin B_{12} absorption with a decrease in serum levels has been observed in patients treated long-term with metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation should be considered [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Hepatobiliary Disorders: *Very rare:* Isolated reports of liver function test abnormalities or hepatitis resolving upon metformin discontinuation.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

Laboratory tests

Ertugliflozin

Increases in serum creatinine and decreases in eGFR
Initial increases in mean creatinine and decreases in mean eGFR in patients treated with ertugliflozin were generally transient during continuous treatment. In the pool of three placebo-controlled clinical trials, mean changes from baseline in creatinine at 6 weeks were 2.41 and 2.76 µmol/L for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.24 µmol/L for placebo. Mean changes from baseline in eGFR were -2.7 and -3.1 mL/min/1.73 m^2 for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.3 mL/min/1.73 m^2 for placebo. At 26 weeks, mean changes from baseline in creatinine were -0.08 and 0.80 µmol/L for ertugliflozin 5 mg and 15 mg, respectively, compared to -0.57 µmol/L for placebo. Mean changes from baseline in eGFR at 26 weeks were 0.5 and -0.6 mL/min/1.73 m^2 for ertugliflozin 5 mg and 15 mg, respectively, compared to 0.7 mL/min/1.73 m^2 for placebo. Patients with moderate renal impairment at baseline had larger mean changes at 6 weeks (approximately 1 mL/min/1.73 m^2) with some attenuation but not a complete return to baseline by 26 weeks. These changes were observed to reverse after treatment discontinuation.

Increases in low-density lipoprotein cholesterol (LDL-C)
In the pool of three placebo-controlled trials, dose-related increases in LDL-C were observed in patients treated with ertugliflozin. Mean percent changes from baseline in LDL-C relative to placebo were 2.6% and 5.4% with ertugliflozin 5 mg and ertugliflozin 15 mg, respectively. The range of mean baseline LDL-C was 2.50 to 2.53 mmol/L across treatment groups.

Increases in haemoglobin
In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline in haemoglobin were 4.6 g/L (3.5%) with ertugliflozin 5 mg, 4.8 g/L (3.5%) with ertugliflozin 15 mg, and -2.1 g/L (-1.4%) with placebo. The range of mean baseline haemoglobin was 139.0 to 140.0 g/L across treatment groups. At the end of treatment, 0.2%, 0.4%, and 0.0% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively, had a haemoglobin increase greater than 20 g/L and above the upper limit of normal. This change in laboratory parameter is of unknown clinical significance.

Increases in serum phosphate
In the pool of three placebo-controlled trials, mean changes (percent changes) from baseline in serum phosphate were 0.07 mmol/L (6.8%) with ertugliflozin 5 mg, 0.08 mmol/L (8.5%) with ertugliflozin 15 mg, and 0.01 mmol/L (1.9%) with placebo. The range of mean baseline serum phosphate was 1.14 to 1.14 mmol/L across treatment groups. In a clinical trial of patients with moderate renal impairment, mean changes (percent changes) from baseline at Week 26 in serum phosphate were 0.09 mmol/L (9.7%) with ertugliflozin 5 mg, 0.08 mmol/L (7.8%) with ertugliflozin 15 mg, and -0.00 mmol/L (0.8%) with placebo. This change in laboratory parameter is of unknown clinical significance.

Adverse reactions in specific populations

Elderly patients

Ertugliflozin
Across the clinical program, a total of 876 (25.7%) patients treated with ertugliflozin were 65 years and older, and 152 (4.5%) patients treated with ertugliflozin were 75 years and older. Patients 65 years and older had a higher incidence of adverse reactions related to volume depletion compared to younger patients; events were reported in 2.2%, 2.6%, and 1.1% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and comparator, respectively [see 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients [See 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Renal impairment

Ertugliflozin
The efficacy and safety of ertugliflozin were evaluated in a study of patients with moderate renal impairment. In this study, 202 patients exposed to ertugliflozin had an eGFR between 45 and 60 mL/min/1.73 m^2 and 111 patients exposed to ertugliflozin had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose-lowering efficacy of ertugliflozin decreased in patients with worsening renal function. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin had increases in serum creatinine and decreases in eGFR, and increased risks for renal-related and volume depletion adverse reactions [see 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Metformin
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. SEGLUROMET is contraindicated in patients with an eGFR below 60 mL/min/1.73 m^2.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

In the event of an overdose with SEGLUROMET, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status.

Ertugliflozin
Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

Removal of ertugliflozin by haemodialysis has not been studied.

Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 g. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]. Metformin is dialyzable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

SEGLUROMET
SEGLUROMET combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: ertugliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Ertugliflozin
SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Patients with diabetes have been shown to have elevated reabsorption of glucose which may result in persistence of hyperglycaemia. Ertugliflozin is an inhibitor of SGLT2 with an IC_{50} of 0.88 nM. It displays >2,200-fold selectivity for SGLT2 over SGLT1 (responsible for glucose absorption in the gut). By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE), which lowers fasting plasma glucose (FPG) and haemoglobin $A1_C$ levels in an insulin-independent manner. Additionally, UGE results in caloric loss and with ensuing weight loss. Ertugliflozin also causes an osmotic diuresis, which may result in reduction of blood pressure. UGE is observed after the first dose. UGE with ertugliflozin depends on plasma glucose levels and glomerular filtration rate. Consequently, UGE is reduced as plasma glucose levels fall, which reduces the risk of hypoglycaemia.

Urinary glucose excretion and urinary volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE), with the 15 mg dose providing incrementally greater UGE relative to the 5 mg dose. Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume. Ertugliflozin acts independently of insulin secretion and insulin action. Over time, significant improvement in beta cell function (HOMA-beta) has been observed in clinical studies with ertugliflozin.

Cardiac electrophysiology
In a randomised, placebo-controlled, active-comparator, crossover study, 42 healthy subjects were administered a single oral supratherapeutic dose of ertugliflozin 100 mg (6.7 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with 100 mg ertugliflozin.

Metformin hydrochloride
Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects [except in special circumstances, see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS] and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

CLINICAL TRIALS

There have been no clinical efficacy studies conducted with SEGLUROMET. However, bioequivalence of SEGLUROMET with coadministered ertugliflozin and metformin tablets was demonstrated.

The efficacy and safety of ertugliflozin in combination with metformin have been studied in 4 multicentre, randomised, double blind, placebo- and active comparator-controlled, Phase 3 clinical studies involving 3,643 patients with type 2 diabetes. These studies included White, Hispanic, Black, Asian, and other racial and ethnic groups, and patients with an age range of 21 to 86 years.

In patients with type 2 diabetes, treatment with ertugliflozin in combination with metformin produced clinically and statistically significant improvements in HbA1c and FPG compared to placebo or active comparator.

In patients with type 2 diabetes treated with ertugliflozin in combination with metformin, the improvement in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline BMI, and duration of type 2 diabetes mellitus.

Ertugliflozin as add-on combination therapy with metformin

A total of 621 patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥1,500 mg/day) participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin in combination with metformin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin therapy.

At Week 26, treatment with ertugliflozin at 5 mg or 15 mg daily provided statistically significant improvements in HbA1c, FPG, and body weight compared to placebo. Treatment with ertugliflozin at 5 mg or 15 mg daily provided a statistically significant improvement in systolic and diastolic blood pressure compared to placebo. Ertugliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo (see Table 3 and Figure 3).

Table 3. Results at Week 26 from a Placebo-Controlled Study for Ertugliflozin Used in Combination with Metformin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	8.06	8.13	8.17
Change from baseline (LS mean†)	-0.73	-0.91	-0.03
Difference from placebo (LS mean†, 95% CI)	-0.70‡ (-0.87, -0.53)	-0.88‡ (-1.05, -0.71)	
Patients [N (%)] with HbA1c <7%	73 (35.3)§	82 (40.0)§	33 (15.8)
FPG (mmol/L)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	9.33	9.32	9.39
Change from baseline (LS mean†)	-1.53	-2.17	-0.05
Difference from placebo (LS mean†, 95% CI)	-1.48‡ (-1.83, -1.14)	-2.12‡ (-2.47, -1.78)	
Body Weight (kg)	**N = 207**	**N = 205**	**N = 209**
Baseline (mean)	84.9	85.3	84.5
Change from baseline (LS mean†)	-3.0	-2.9	-1.3
Difference from placebo (LS mean†, 95% CI)	-1.7‡ (-2.2, -1.1)	-1.6‡ (-2.2, -1.0)	
Systolic Blood Pressure (mmHg)	**N = 207**	**N = 204**	**N = 209**
Baseline (mean)	130.5	130.2	129.3
Change from baseline (LS mean†)	-4.4	-5.2	-0.7
Difference from placebo (LS mean†, 95% CI)	-3.7¶ (-6.0, -1.4)	-4.5‡ (-6.8, -2.2)	
Diastolic Blood Pressure (mmHg)	**N = 207**	**N = 204**	**N = 209**
Baseline (mean)	78.4	78.1	77.4
Change from baseline (LS mean†)	-1.6	-2.2	0.2
Difference from placebo (LS mean†, 95% CI)	-1.8¶ (-3.2, -0.4)	-2.4‡ (-3.9, -1.0)	
Efficacy in patients with high baseline HbA1c (≥9%)			
HbA1c (%)	**N = 34**	**N = 38**	**N = 40**
Baseline (mean)	9.47	9.62	9.49
Change from baseline (LS mean#)	-1.61	-1.73	-0.30
Difference from placebo (LS mean#, 95% CI)	-1.31 (-1.73, -0.90)	-1.43 (-1.83, -1.03)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.

† Least squares means adjusted for treatment, time, prior anti-hyperglycaemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, premenopausal women, women who are perimenopausal or <3 years postmenopausal, women who are ≥3 years postmenopausal) and the interaction of time by treatment.

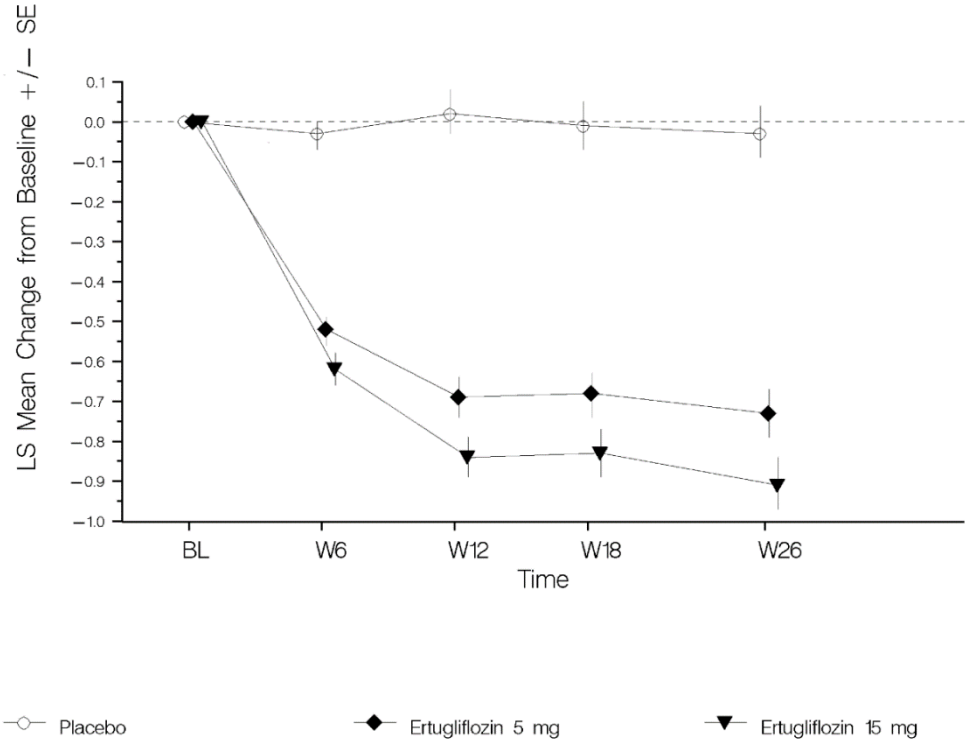
‡ p≤0.001 compared to placebo.

§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

¶ p<0.05 compared to placebo.

Obtained from a repeated measures ANCOVA model with terms for prior antihyperglycaemic medication, menopausal status stratum, baseline eGFR, baseline HbA1c, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions.

Figure 3 HbA1c (%) Change over Time in a 26-Week Placebo-Controlled Study for Ertugliflozin Used in Combination with Metformin*



* Based on the full analysis set population, which included all randomised, treated patients with at least one HbA1c measurement.

Factorial study with ertugliflozin and sitagliptin (JANUVIA) as add-on combination therapy with metformin

A total of 1,233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre, 26-week, active-controlled study to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥1,500 mg/day) were randomised to one of five active-treatment arms: ertugliflozin 5 mg or 15 mg, JANUVIA 100 mg, or JANUVIA 100 mg in combination with 5 mg or 15 mg ertugliflozin administered once daily in addition to continuation of background metformin therapy.

At Week 26, ertugliflozin 5 mg or 15 mg used in combination with JANUVIA 100 mg provided statistically significant improvement in HbA1c and FPG compared to the individual components (see Table 4). More patients receiving ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg achieved an HbA1c <7% compared to the individual components. Treatment with ertugliflozin 5 mg or 15 mg in combination with JANUVIA 100 mg also resulted in a statistically significant reduction in body weight and systolic blood pressure compared to JANUVIA 100 mg.

Table 4. Results at Week 26 from a Factorial Study with Ertugliflozin and Sitagliptin as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.57	8.57	8.50	8.56	8.56
Change from baseline (LS mean†)	-1.02	-1.08	-1.05	-1.49	-1.52
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean†, 95% CI)				-0.43‡ (-0.60, -0.27) -0.46‡ (-0.63, -0.30)	-0.47‡ (-0.63, -0.30) -0.44‡ (-0.61, -0.27)
Patients [N (%)] with HbA1c <7%	66 (26.4)	79 (31.9)	81 (32.8)	127§ (52.3)	120§ (49.2)
FPG (mmol/L)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	10.22	9.96	9.85	10.20	9.83
Change from baseline (LS mean†)	-1.98	-2.05	-1.42	-2.44	-2.70
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean†, 95% CI)				-1.02‡ (-1.33, -0.71) - 0.46¶ (-0.77, -0.15)	-1.28‡ (-1.60, -0.97) -0.65‡ (-0.96, -0.35)
Body Weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from Sitagliptin (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)
Systolic Blood Pressure (mmHg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	129.7	128.9	128.3	130.2	129.1
Change from baseline (LS mean†)	-3.9	-3.7	-0.7	-3.4	-3.7
Difference from Sitagliptin (LS mean†, 95% CI)				-2.8¶ (-4.7, -0.8)	-3.0¶ (-4.9, -1.1)
Efficacy in patients with high baseline HbA1c (≥10%)					
HbA1c (%)	**N = 25**	**N = 21**	**N = 26**	**N = 20**	**N = 22**
Baseline (mean)	10.66	10.51	10.46	10.46	10.39
Change from baseline (LS mean#)	-2.10	-1.30	-1.82	-2.35	-2.66
Difference from Sitagliptin Ertugliflozin 5 mg Ertugliflozin 15 mg (LS mean#, 95% CI)				-0.53 (-1.08, -0.03) -0.24 (-0.80, -0.32)	-0.84 (-1.38, -0.30) -1.36 (-1.91, -0.81)

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, baseline eGFR and the interaction of time by treatment.
‡ p<0.001 compared to control group.

§ p<0.001 compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p≤0.005 compared to control group.
# Obtained from a repeated measures ANCOVA model adjusted for baseline eGFR, baseline HbA1c, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions.

Ertugliflozin as add-on combination therapy with metformin and sitagliptin (JANUVIA)

A total of 463 patients with type 2 diabetes inadequately controlled on metformin (≥1,500 mg/day) and JANUVIA 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and JANUVIA therapy.

At Week 26, treatment with ertugliflozin at 5 mg or 15 mg daily provided statistically significant improvements in HbA1c, FPG, body weight, and systolic blood pressure compared to placebo. Ertugliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo (see Table 5).

Table 5. Results at Week 26 from an Add-on Study of Ertugliflozin in Combination with Metformin and Sitagliptin*

	Ertugliflozin 5 mg	**Ertugliflozin 15 mg**	**Placebo**
HbA1c (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.05	8.00	8.03
Change from baseline (LS mean†)	-0.78	-0.86	-0.09
Difference from placebo (LS mean†, 95% CI)	-0.69‡ (-0.87, -0.50)	-0.76‡ (-0.95, -0.58)	
Patients [N (%)] with HbA1c <7%	50 (32.1)§	61 (39.9)§	26 (17.0)
FPG (mmol/L)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	9.31	9.53	9.41
Change from baseline (LS mean†)	-1.49	-1.83	-0.10
Difference from placebo (LS mean†, 95% CI)	-1.40‡ (-1.82, -0.97)	-1.74‡ (-2.16, -1.31)	
Body Weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	
Systolic Blood Pressure (mmHg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	132.1	131.6	130.2
Change from baseline (LS mean†)	-3.8	-4.8	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.9¶ (-5.4, -0.5)	-3.9¶ (-6.4, -1.5)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication.
‡ p≤0.001 compared to placebo.
§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p<0.05 compared to placebo.

Active-controlled study of ertugliflozin versus glimepiride as add-on combination therapy with metformin

A total of 1,326 patients with type 2 diabetes inadequately controlled on metformin monotherapy participated in a randomised, double-blind, multi-centre, 52-week, active comparator-controlled study to evaluate the efficacy and safety of ertugliflozin in combination with metformin. These patients, who were receiving metformin monotherapy (≥1,500 mg/day), were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or glimepiride administered once daily in addition to continuation of background metformin therapy. Glimepiride was initiated at 1 mg/day and titrated up to a maximum dose of 6 or 8 mg/day (depending on maximum approved dose in each country) or a maximum tolerated dose or down-titrated to avoid or manage hypoglycaemia. The mean daily dose of glimepiride was 3.0 mg.

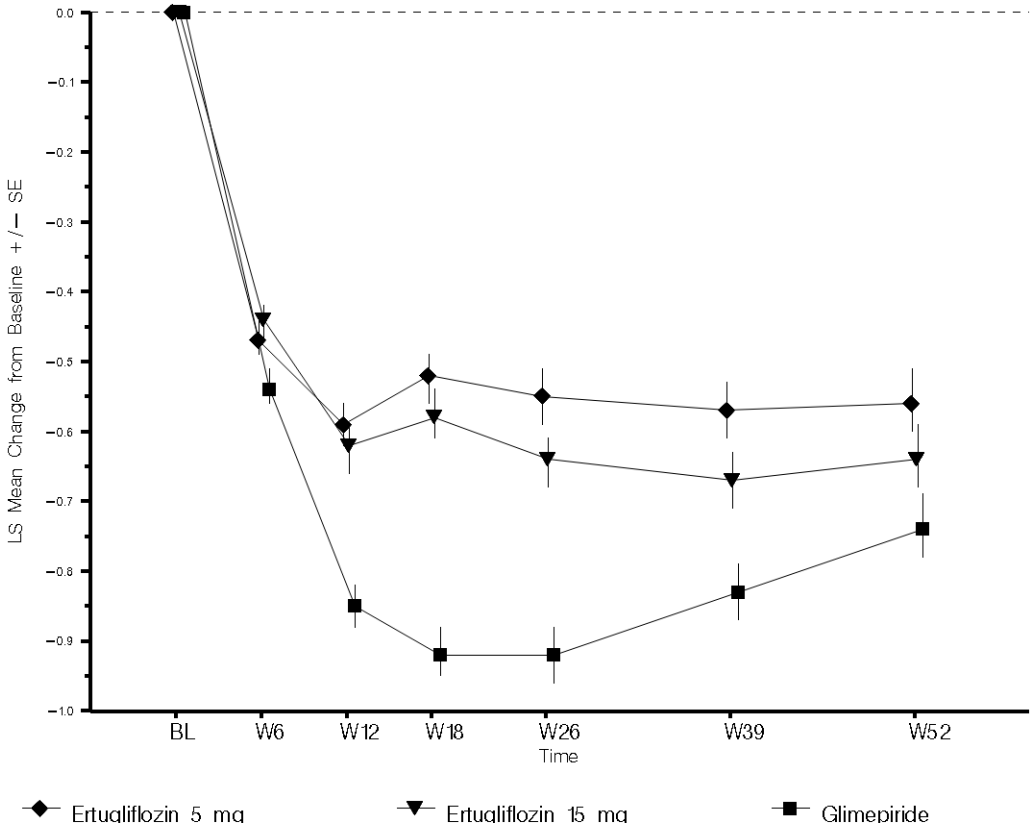
At Week 52, ertugliflozin 5 mg and 15 mg provided similar reductions in HbA1c from baseline compared to glimepiride when added to metformin therapy. Ertugliflozin 15 mg was non-inferior to glimepiride after 52 weeks of treatment. At Week 52, ertugliflozin 15 mg resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.4 kg for ertugliflozin 15 mg vs. +0.9 kg for glimepiride; treatment difference -4.3 kg; p<0.001). (See Table 6 and Figure 4.)

Table 6. Results at Week 52 from an Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on Therapy in Patients Inadequately Controlled on Metformin*

	Ertugliflozin 5 mg	**Ertugliflozin 15 mg**	**Glimepiride**
HbA1c (%)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	7.81	7.80	7.76
Change from baseline (LS mean†)	-0.656	-0.64	-0.74
Difference from glimepiride (LS mean†, 95% CI)	0.18‡ (0.06, 0.30)	0.10§(-0.02, 0.22)	
Patients [N (%)] with HbA1c <7%	154 (34.4)	167 (38.0)	190 (43.5)
Body Weight (kg)	**N = 448**	**N = 440**	**N = 437**
Baseline (mean)	87.9	85.6	86.8
Change from baseline (LS mean†)	-3.0	-3.4	0.9
Difference from glimepiride (LS mean†, 95% CI)	-3.9 (-4.4, -3.4)	-4.3¶ (-4.8, -3.8)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication (monotherapy or dual therapy), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.
‡ Non-inferiority between ertugliflozin 5 mg and glimepiride was not established.
§ Non-inferiority is declared when the upper bound of the two-sided 95% confidence interval (CI) for the mean difference is less than 0.3%.
¶ p<0.001 compared to glimepiride.

Figure 4 HbA1c (%) Change over Time in an Active-Controlled Study Comparing Ertugliflozin to Glimepiride as Add-on Therapy in Patients Inadequately Controlled on Metformin*



* Based on the full analysis set population, which included all randomised, treated patients with at least one HbA1c measurement.

5.2 PHARMACOKINETIC PROPERTIES

SEGLUROMET
SEGLUROMET has been shown to be bioequivalent to coadministration of corresponding doses of ertugliflozin and metformin tablets.

Ertugliflozin
The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes. The steady-state mean area under the curve (AUC) and peak concentration (C_{max}) were 398 ng·hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1,193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption

SEGLUROMET
The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and metformin when administered as SEGLUROMET tablets are comparable to those reported for the individual tablets. Food had no meaningful effect on AUC_{inf} of ertugliflozin or metformin, but reduced

mean ertugliflozin C_{max} by approximately 41% and metformin C_{max} by approximately 29% compared to the fasted condition.

Ertugliflozin
Following single dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median T_{max}) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose proportional manner following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, ertugliflozin was administered without regard to meals.

Metformin hydrochloride
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Ertugliflozin
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 85.5 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Metformin hydrochloride
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Ertugliflozin
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O glucuronidation to two glucuronides. These are present in plasma at levels 2- and 4-times lower than ertugliflozin and are pharmacologically inactive at clinically relevant concentrations. CYP mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Metformin hydrochloride
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Ertugliflozin
The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Metformin hydrochloride
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations

Renal impairment

SEGLUROMET
Studies characterising the pharmacokinetics of ertugliflozin and metformin after administration of SEGLUROMET in renally impaired patients have not been performed [see 4.2 DOSE AND METHOD OF ADMINISTRATION].

Ertugliflozin
In a Phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by estimated glomerular filtration rate (eGFR)), following a single-dose administration of 15 mg SEGLUROMET, the mean increases in AUC of ertugliflozin were ≤1.7-fold, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of

renal impairment [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Metformin hydrochloride
In patients with decreased renal function (based on measured eGFR), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in eGFR [see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Hepatic impairment

Ertugliflozin
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

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

Paediatric
No studies with SEGLUROMET have been performed in paediatric patients.

Effects of age, body weight, gender, and race

Ertugliflozin
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

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.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ertugliflozin
Ertugliflozin was not mutagenic in the bacterial reverse mutation assay, *in vitro* (cytogenetic assay in human lymphocytes), or *in vivo* (rat bone marrow micronucleus test).

Metformin hydrochloride
There was no evidence of a genotoxic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity

No carcinogenicity studies have been conducted with ertugliflozin and metformin in combination.

Ertugliflozin
The carcinogenic potential of ertugliflozin was examined in 2-year studies in mice and rats. Administration was by oral gavage. There were no ertugliflozin-related neoplastic findings in mice at doses up to 40 mg/kg/day (approximately 41 times human exposure at the MRHD of 15 mg/day based on plasma AUC for unbound ertugliflozin) or in female rats at doses up to 15 mg/kg/day (approximately 50 times human exposure), the highest dose levels tested. In male rats, treatment with ertugliflozin at 15 mg/kg/day increased the incidence of benign adrenal medullary phaeochromocytoma. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis and is not considered relevant to human risk. The no-observed-effect level (NOEL) for neoplasia in male rats was 5 mg/kg/day (approximately 13 times human exposure at the MRHD of 15 mg/day) and no neoplasia was observed in female rats.

Metformin hydrochloride
Long term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of SEGLUROMET contains the following inactive ingredients: povidone, microcrystalline cellulose, crospovidone, sodium lauryl sulfate, magnesium stearate, and carnauba wax.

The film coating contains: hypromellose, hyprolose, titanium dioxide, and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC. Store in original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in aluminium/ aluminium blister packs of 14 tablets (starter packs) and 56 tablets.

Not all packs may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

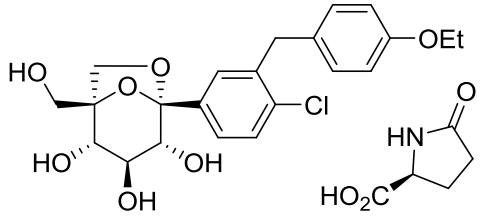
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

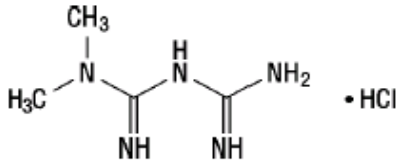
Ertugliflozin
SEGLUROMET tablets contain ertugliflozin pyroglutamic acid, the isolated form of the active ingredient ertugliflozin. The chemical name of ertugliflozin pyroglutamic acid is (1*S*,2*S*,3 *S*,4*R*,5*S*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2*S*)-5-oxopyrrolidine-2-carboxylic acid. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00.

The chemical structure is:



Ertugliflozin pyroglutamic acid is a white to off-white powder that is soluble in ethyl alcohol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water.

Metformin hydrochloride
Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycaemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

CAS number

Ertugliflozin
The CAS Registry Number is 1210344-83-4.

Metformin hydrochloride
The CAS Registry Number is 1115-70-4.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Rd
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

15-May-2018

10 DATE OF REVISION

8-July-2019

Summary table of changes

Section changed	Summary of new information
4.4	Update to the Limb amputation subsection