PROFESSIONAL INFORMATION for

SYNGLUTRA 5/500; 5/1 000; 10/500; 10/1 000

Extended Release Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SYNGLUTRA 5/500 Extended Release Tablets

SYNGLUTRA 5/1 000 Extended Release Tablets

SYNGLUTRA 10/500 Extended Release Tablets

SYNGLUTRA 10/1 000 Extended Release Tablets

SYNGLUTRA IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. SYNGLUTRA IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious, life-threatening or fatal, in patients taking SYNGLUTRA.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. SYNGLUTRA should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with SYNGLUTRA.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting

from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. SYNGLUTRA is contraindicated in these patients.

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.

If acidosis is suspected, SYNGLUTRA should be discontinued and the patient hospitalised immediately (see section 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYNGLUTRA 5/500: Each film coated tablet contains the equivalent of 5 mg dapagliflozin (as dapagliflozin propanediol) and 500 mg of metformin hydrochloride.

Inactive ingredients are carboxymethylcellulose sodium, copovidone, crospovidone, ferric oxide red, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide and Opadry II 85F17424 Beige film coating (containing ferrosoferric oxide, iron oxide red, iron oxide yellow, macrogol, part hydrolysed polyvinyl alcohol, talc, titanium dioxide).

Contains mannitol (84 mg/tablet).

SYNGLUTRA 5/1 000: Each film coated tablet contains the equivalent of 5 mg dapagliflozin (as dapagliflozin propanediol) and 1 000 mg of metformin hydrochloride.

Inactive ingredients are carboxymethylcellulose sodium, copovidone, crospovidone, ferric oxide red, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon

dioxide and Opadry II 85F565267 Brown film coating (containing iron oxide red, iron oxide yellow, macrogol, part hydrolysed polyvinyl alcohol, talc, titanium dioxide).
Contains mannitol (84 mg/tablet).

SYNGLUTRA 10/500: Each film coated tablet contains the equivalent of 10 mg dapagliflozin (as dapagliflozin propanediol) and 500 mg of metformin hydrochloride.
Inactive ingredients are carboxymethylcellulose sodium, copovidone, crospovidone, ferric oxide yellow, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide and Opadry II 85F510122 Green film coating (containing FD&C Blue #2/Indigo carmine, iron oxide yellow, macrogol, part hydrolysed polyvinyl alcohol, talc, titanium dioxide).
Contains mannitol (84 mg/tablet).

SYNGLUTRA 10/1 000: Each film coated tablet contains the equivalent of 10 mg dapagliflozin (as dapagliflozin propanediol) and 1 000 mg of metformin hydrochloride.
Inactive ingredients are carboxymethylcellulose sodium, copovidone, crospovidone, ferric oxide yellow, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide and Opadry II 85F94245 Pink film coating (containing iron oxide red, macrogol, part hydrolysed polyvinyl alcohol, talc, titanium dioxide).
Contains mannitol (84 mg/tablet).

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Extended Release Tablets.
SYNGLUTRA 5/500: Beige, biconvex, capsule-shaped, film coated tablets, “C394" debossed on one side and plain on the reverse side.

SYNGLUTRA 5/1 000: Brown, biconvex, oval shaped, film coated tablets, "C396" debossed on one side and plain on the reverse side.

SYNGLUTRA 10/500: Green, biconvex, capsule-shaped, film coated tablets, "C395" debossed on one side and plain on the reverse side.

SYNGLUTRA 10/1 000: Pink, biconvex, oval-shaped, film coated tablets, "C397" debossed on one side and plain on the reverse side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SYNGLUTRA is indicated in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate:

- for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise.
- to reduce the risk of developing new or worsening existing heart failure or cardiovascular death in Type 2 diabetic mellitus patients with established cardiovascular (CV) disease or multiple CV risk factors.

4.2. Posology and method of administration

Posology

The recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin is 500 mg once daily, which can be titrated to 2000 mg once daily, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dose of SYNGLUTRA should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose.

If no adequate strength of SYNGLUTRA is available, individual mono-components should be used instead of the fixed dose combination.

It is recommended to not exceed a dose of dapagliflozin 10 mg daily (two tablets of 5 mg dapagliflozin / 500 mg metformin or two tablets of 5 mg dapagliflozin / 1000 mg metformin).

Special populations

Patients with renal impairment

Assess renal function prior to initiation of SYNGLUTRA and periodically thereafter (see **section 4.4** and **5.2**).

Renal impaired patients may have a higher incidence of adverse events.

Table 1 Dosage in patients with renal impairment

eGFR ml/min/ 1,73 m^2*	**Metformin XR**	**Dapagliflozin**
60-89	Maximum daily dose is 2 000 mg Dose reduction may be considered in relation to declining renal function	Maximum total daily dose is 10mg
45-59	Maximum daily dose is 2 000 mg The starting dose is at most half of the maximum dose	Maximum total daily dose is 10 mg
30-44	Maximum daily dose is 1 000 mg The starting dose is at most half of the maximum dose	Dapagliflozin is not recommended when eGFR is persistently below 45 mL/min/1,73 m^2
<30	Metformin is contraindicated	Dapagliflozin is contraindicated

Mild renal impairment

No dosage adjustment for SYNGLUTRA is required for mild renal impairment (defined as eGFR < 60 - 89 mL/min/1,73 m^2 by Modified Diet in Renal Disease (MDRD) eGFR equation).

Moderate renal impairment

SYNGLUTRA is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1,73 m^2 (see **section 4.4**).

No dose adjustment is required for patients with eGFR ≥ 45 mL/ min/1,73 m^2.

Severe renal impairment

Due to the metformin component, SYNGLUTRA is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1,73 m^2) (see **section 4.3**).

Hepatic impairment

SYNGLUTRA must be avoided in patients with clinical or laboratory evidence of hepatic impairment since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin (see **section 4.4**).

Patients at risk for volume depletion

For patients at risk for volume depletion due to co-existing conditions, a 5 mg starting dose of dapagliflozin may be appropriate.

Elderly patients

Because metformin, as in SYNGLUTRA, is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, SYNGLUTRA should be used with caution as age increases. The renal function recommendations provided for all patients also apply to elderly patients.

Paediatric population

Paediatric and adolescent patients

The safety and efficacy of SYNGLUTRA in paediatric and adolescent patients have not been

established. No data are available.

Method of administration

SYNGLUTRA should be taken once daily in the morning with food to reduce the gastrointestinal (GI) side effects due to metformin.

SYNGLUTRA tablets must be swallowed whole and never crushed, cut, or chewed.
Occasionally, the inactive ingredients of SYNGLUTRA will be eliminated in the faeces as a soft, hydrated mass that may resemble the original tablet.

4.3. Contraindications

SYNGLUTRA is contraindicated in patients with:

- Hypersensitivity to dapagliflozin, metformin hydrochloride or any of the inactive ingredients of SYNGLUTRA.
- Any type of acute or chronic metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, with or without coma). Diabetic ketoacidosis should be treated with insulin.
- Diabetic pre-coma.
- Severe renal impairment (eGFR < 30 mL/min/1,73m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, or shock, intravascular administration of iodinated contrast media.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, pancreatitis, recent myocardial infarction or shock.
- Hepatic impairment (see **section 4.2** and **section 4.4**).
- Acute alcohol intoxication, alcoholism (acute or chronic).
- Diabetes mellitus type 1.
- Pregnant women or women who are breastfeeding their babies (see **section 4.6**).

4.4. Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is associated with the use of SYNGLUTRA. Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation (metformin) plasma levels generally > 5 mcg/l) Metformin, as in SYNGLUTRA, 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), SYNGLUTRA should be temporarily discontinued and contact with a healthcare professional is recommended.

In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and SYNGLUTRA therapy should be stopped. Lactic acidosis is a medical emergency, which must be treated in hospital. SYNGLUTRA is excreted by the kidney and regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus.

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients receiving SYNGLUTRA. 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 medicines that may cause lactic acidosis (see **section 4.3** and **section 4.5**).

Patients and/or caregivers should be informed on the risk of lactic acidosis.

Diagnosis

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. 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. If metabolic acidosis is suspected, SYNGLUTRA should be discontinued and the patient should be hospitalised immediately.

Renal function

The efficacy of dapagliflozin, as in SYNGLUTRA, 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 4.3**). Therefore, SYNGLUTRA should not be initiated in patients with GFR < 60 mL/min and should be discontinued at GFR persistently below 45mL/min.

Metformin, as in SYNGLUTRA, is excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment of renal function.

Renal function should be assessed:

- Before initiation of treatment and regularly thereafter (see **section 4.2** and **section 4.8**).
- At least annually in patients with normal renal function.
- At least two to four times a year in patients with renal function where eGFR levels are approaching 45 mL/min/1,73 m^2 and in elderly patients.
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- If renal function falls below GFR < 45 mL/min, treatment should be discontinued.
- SYNGLUTRA is contraindicated in patients with GFR of < 30 mL/min and should be

temporarily discontinued 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 antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID.

Hepatic function

Since impaired hepatic function has been associated with some cases of metformin-associated lactic acidosis, SYNGLUTRA should be avoided in patients with clinical or laboratory evidence of hepatic disease.

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

SYNGLUTRA may cause a decrease in systolic blood pressure and diastolic blood pressure.

Due to its mechanism of action, dapagliflozin as in SYNGLUTRA, increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations.

The diuretic effect of SYNGLUTRA is a potential concern for volume depleted patients. There is limited experience in clinical trials in patients at increased risk for volume depletion.

SYNGLUTRA is not recommended for use in patients receiving loop diuretics (see **section 4.5**) or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). SYNGLUTRA should be permanently discontinued in patients who develop volume depletion

(see **section 4.8**).

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

For patients receiving SYNGLUTRA, 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 SYNGLUTRA is recommended for patients who develop volume depletion until the depletion is corrected (see **section 4.8**).

The use of SYNGLUTRA is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake. Patients on long-term treatment with SYNGLUTRA should have an annual estimation of vitamin B_{12} levels, since SYNGLUTRA may cause malabsorption of vitamin B_{12}, which may result in megaloblastic anaemia.

Excessive alcohol intake

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving SYNGLUTRA.

Diabetic ketoacidosis

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

There have been post-marketing reports of ketoacidosis and diabetic ketoacidosis (DKA), including life-threatening and fatal cases, in patients treated with SGLT2 inhibitors, including dapagliflozin, as in SYNGLUTRA. In a number of cases, the presentation of the condition

was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of dapagliflozin, as in SYNGLUTRA.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, malaise, 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, SYNGLUTRA should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with SYNGLUTRA may be restarted once the patient's condition has stabilised.

Before initiating SYNGLUTRA, 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 1 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis or pancreatic surgery], 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, including SYNGLUTRA is not indicated in these patients.

Restarting SGLT2 inhibitor, including SYNGLUTRA, treatment in patients with previous DKA

while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

SYNGLUTRA is contraindicated for the treatment of patients with type 1 diabetes mellitus (see **section 4.3**).

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 448 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 or perineal abscess may precede necrotising fasciitis. If Fournier’s gangrene is suspected, SYNGLUTRA should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

Urinary tract infections may be reported more frequently for SYNGLUTRA. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of SYNGLUTRA should be considered when treating pyelonephritis or urosepsis (see s**ection 4.8**).

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with antihypertensive medicines that may cause changes in renal function, such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see **section 4.3** and **section 4.8**).

Cardiac failure

Clinical data in patients with New York Heart Association (NYHA) class I – II is limited, and there is no clinical data with dapagliflozin, as in SYNGLUTRA, in NYHA class III – IV.

Use with medicines known to cause hypoglycaemia

Insulin and insulin secretagogues, such as sulphonylureas, may cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin, as in SYNGLUTRA (see **section 4.8**).

Hypoglycaemia does not usually occur in patients receiving metformin alone under usual circumstances, but may occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering medicines (such as sulphonylureas 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 recognise in the elderly and in people who are taking beta-adrenergic blocking medicines.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) is documented in long-term studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class

effect. It is important to counsel patients on routine preventative foot care.

Urine laboratory assessments

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

Administration of iodinated contrast media

The intravascular administration of iodinated contrast materials in radiological studies (such as intravenous urography and intravenous angiography) can lead to contrast induced nephropathy or renal failure, which may result in metformin, as in SYNGLUTRA, accumulation and increased risk of lactic acidosis. SYNGLUTRA should be discontinued prior to, or at the time of the imaging procedure and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see **section 4.3** and **section 4.5**).

Surgery

SYNGLUTRA should be discontinued 48 hours before elective 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 haemodynamic and acid-base status have been re-evaluated and found to be stable.

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combination therapy may cause hypoglycaemia. Stabilisation of diabetic patients with SYNGLUTRA and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the medicines has been obtained (see **section 4.3**).

Change in clinical status of patients with previously controlled type 2 diabetes

As SYNGLUTRA contains metformin, a patient with type 2 diabetes previously well-controlled on it who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

Paediatric use

Safety and efficacy of SYNGLUTRA in paediatric patients has not been established.

4.5. Interaction with other medicines and other forms of interaction

Coadministration of multiple doses of dapagliflozin and metformin, as in SYNGLUTRA, does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy patients. No interaction studies have been performed for SYNGLUTRA**.** The following statements reflect the information available on the individual active substances.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

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

Insulin and insulin secretagogues:

Insulin and insulin secretagogues, such as sulphonylureas, may cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the

risk of hypoglycaemia when used in combination with dapagliflozin, as in SYNGLUTRA (see **section 4.2** and **section 4.8**).

Pharmacokinetic interactions

The metabolism of dapagliflozin, as in SYNGLUTRA, is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin, as in SYNGLUTRA**,** and dapagliflozin 3-O-glucuronide 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 medicines that are metabolised by these enzymes.

Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O-glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitor of dapagliflozin 3-O-glucuronide formation by UGT1A9 (IC50 = 32 µM).

Effects of other medicines on dapagliflozin

The pharmacokinetics of dapagliflozin may not be altered by metformin (an hOCT-1 and hOCT-2), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate),

voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan or simvastatin (a CYP3A4 substrate).

Following coadministration of dapagliflozin, as in SYNGLUTRA with rifampicin (an inducer of various active transporters and medicine metabolising enzymes) a 22 % decrease in dapagliflozin systemic exposure (AUC) may be 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, phenobarbital) is not expected.

Following coadministration of dapagliflozin, as in SYNGLUTRA with mefenamic acid (an inhibitor of UGT1A9), a 51 % increase in dapagliflozin systemic exposure may occur, with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicines

Dapagliflozin may not alter the pharmacokinetics of metformin, pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a hOAT 3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C19 substrate, R-warfarin), or the anticoagulatory effects of warfarin as measured by the prothrombin time [International Normalised Ratio (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.

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of SYNGLUTRA have not been studied.

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

Monitoring glycaemic control with 1,5-AG assay should not be used as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors, including SYNGLUTRA. Use alternative methods to monitor glycaemic control.

Metformin

Concomitant use not recommended

Cationic medicines that are eliminated by renal tubular secretion (e.g. amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim or vancomycin) may interact with metformin, as in SYNGLUTRA, 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 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. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended dosage and directions and changes in diabetic treatment should be considered when cationic medicines that are eliminated by renal tubular secretion are co-administered.

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 contained in SYNGLUTRA (see **section 4.4**). Consumption of alcohol and medicines containing alcohol should be avoided.

Iodinated contrast medicines

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin, as in SYNGLUTRA, accumulation and increased risk of lactic acidosis. SYNGLUTRA should be discontinued prior to, or at the time of the imaging procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see **section 4.3** and **section 4.4**).

Combination requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, diuretics and phenothiazines, thyroid medicines, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers and isoniazid have intrinsic hyperglycaemic activity. Medical practitioners should inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, the dosage of SYNGLUTRA should be adjusted during therapy with the other medicine and upon its discontinuation.

Some medicines 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 medicines in combination with metformin, as in SYNGLUTRA, close monitoring of renal function is necessary. SYNGLUTRA is not recommended for use in patients receiving loop diuretics.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of SYNGLUTRA should be adjusted during therapy with the other medicine and upon its discontinuation.

Vitamins

Long-term treatment with SYNGLUTRA may cause vitamin B_{12} malabsorption in the gastrointestinal tract, thus a dose reduction of SYNGLUTRA should be considered.

4.6. Fertility, pregnancy and lactation

Pregnancy

SYNGLUTRA is contraindicated in pregnancy (see **section 4.3**).

Maternal exposure to dapagliflozin, as in SYNGLUTRA, in rat studies has been associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, SYNGLUTRA should be discontinued.

There are limited amount of data from the use of metformin, as in SYNGLUTRA, in pregnant women.

Breastfeeding

SYNGLUTRA should not be used while breastfeeding (see **section 4.3**).

Studies in rats have shown excretion of dapagliflozin, as in SYNGLUTRA, in milk, as well as pharmacologically-mediated effects in nursing offspring. Exposure to SYNGLUTRA must be avoided during the first 2 years of life.

Metformin is excreted in human milk in small amounts. A risk to babies cannot be excluded.

Fertility

The effect of SYNGLUTRA on fertility in humans has not been studied.

4.7. Effects on ability to drive and use machines

Dapagliflozin or metformin, as contained in SYNGLUTRA, have no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when SYNGLUTRA is used in combination with other glucose-lowering medicines known to cause hypoglycaemia.

4.8. Undesirable effects

SYNGLUTRA has been demonstrated to be bioequivalent with co-administered dapagliflozin and metformin. There have been no therapeutic clinical trials conducted with SYNGLUTRA tablets.

Infections and infestations

Frequent:	Vulvovaginitis, balanitis and related genital infections, including vulvovaginal mycotic infection, vaginal infection, fungal genital infection, vulvovaginal candidiasis, balanitis candida, genital candidiasis, genital infection, male genital infection, penile infection, vulvitis, bacterial vaginitis, vulval abscess, balanoposthitis, genitourinary tract infection, penile abscess and posthitis. Urinary tract infection, including pyelonephritis, cystitis, *Escherichia* urinary tract infection, trigonitis, urethritis, kidney infection and prostatitis. Nasopharyngitis, influenza, pharyngitis.
Less frequent:	Fungal infection.

Immune system disorders

Frequent:	Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity).

Metabolism and nutrition disorders

Frequent:	Hypoglycaemia (when used with sulphonylurea or insulin).
Less frequent:	Volume depletion, dehydration, hypovolaemia, hypotension, thirst, diabetic ketoacidosis, lactic acidosis (see **section 4.4**), vitamin B_{12} deficiency (associated with long-term treatment with metformin due to a decrease in vitamin B_{12} absorption which may result in clinically significant vitamin B_{12} deficiency, or megaloblastic anaemia, less frequently).

Nervous system disorders

Frequent:	Taste disturbance, dizziness, headache.

Gastrointestinal disorders

Frequent:	Gastrointestinal symptoms, including nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.
Less frequent:	Constipation, dry mouth.

Hepatobiliary disorders

Less frequent:	Liver function test abnormalities, or hepatitis resolving on treatment discontinuation.

Skin and subcutaneous tissue disorders

Frequent:	Rash, including generalised rash, pruritic rash, macular, maculopapular, pustular, vesicular and erythematous rash.
Less frequent:	Hyperhidrosis, skin reactions such as erythema, pruritus and urticaria.

Musculoskeletal, connective tissue and bone disorders

Frequent: Back pain.

Renal and urinary disorders

Frequent: Glucosuria, dysuria, polyuria, including pollakiuria, increased urine output and osmotic diuresis.

Less frequent: Nocturia, renal impairment.

Reproductive system and breast disorders

Less frequent: Vulvovaginal pruritus, genital pruritus.

Investigations

Frequent: Dyslipidaemia, increased haematocrit, decreased creatinine renal clearance, hyperphosphatemia.

Less frequent: Increased blood creatine, increased blood urea, decreased weight.

Post-marketing adverse events

Skin and subcutaneous tissue disorders

Frequency unknown: Rash, generalised rash, pruritic rash, macular rash, maculo-papular rash, pustular rash, vesicular rash, erythematous rash.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04**

Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com

4.9. Overdose

In overdose, side effects may be elicited or exacerbated. Appropriate symptomatic and supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin, as in SYNGLUTRA, 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 hospital. The most effective method to remove metformin, as in SYNGLUTRA, and lactate is haemodialysis. Events of hypoglycaemia have been reported with overdoses of metformin.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Medicines used in diabetes, Combinations of oral blood glucose-lowering medicines, ATC code: A10BD15.

Pharmacological classification: A21.2 Oral hypoglycaemics

Mechanism of action

SYNGLUTRA combines two anti-hyperglycaemic medicines with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a potent, selective and reversible inhibitor of sodium glucose co-transporter

2 (SGLT2). SGLT2 is selectively expressed in the kidney and is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) which may be observed after the first dose, may be continuous over the 24-hour dosing interval and sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) may be observed with dapagliflozin.

Urinary glucose excretion (glycosuria) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction may be body fat loss, including visceral fat rather than lean tissue or fluid loss which may be demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 1400 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore may not

produce hypoglycaemia.

Metformin may act via three mechanisms:

- Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by increasing glucose sensitivity, improving peripheral glucose uptake and utilisation.
- Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters.

5.2. Pharmacokinetic properties

SYNGLUTRA combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride extended release administered together as individual tablets.

Interaction with food

The administration of SYNGLUTRA after a high fat meal compared to after the fasted state may result in the same extent of exposure for both dapagliflozin and metformin extended release. The meal may result in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 35 % of dapagliflozin and 17 % of metformin. These changes may not be considered clinically meaningful.

Dapagliflozin

Absorption

Dapagliflozin was absorbed after oral administration and can be administered with or without

food. Maximum dapagliflozin plasma concentrations (C_{max}) may be attained within 2 hours after administration in the fasted state. The C_{max} and AUC values may increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %.

Distribution

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

Metabolism

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounts for 61 % of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant medicine-related component in human plasma, accounting for 42 % [based on $AUC_{(0\text{-}12\ h)}$] of total plasma radioactivity, similar to the 39 % contribution by parent compound. No other metabolite accounts for > 5 % of the total plasma radioactivity at any time point. 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 may be a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is 12,9 hours following a single oral dose of dapagliflozin 10 mg. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. Following administration

of a 50 mg [^{14}C]-dapagliflozin dose, 96 % may be recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose may be excreted as parent compound.

Linearity

Dapagliflozin exposure increases proportional to the increment in dapagliflozin dose over the range of 0,1 to 500 mg and its pharmacokinetics does not change with time upon repeated daily dosing.

Metformin

Absorption

Following a single oral dose of metformin 500 mg extended release tablet, peak plasma levels (C_{max}) may be achieved with a median value of 7 hours and a range of 4 to 8 hours.

At steady-state, both C_{max} and AUC are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily.

Peak plasma levels are approximately 0,6, 1,1, 1,4, and 1,8 µg/mL for 500, 1 000, 1 500, and 2 000 mg once-daily doses, respectively.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin 850 mg averages 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.

Metabolism

Metformin is eliminated unchanged in the urine. No metabolite has been identified in humans. There is no biliary excretion.

Elimination

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 compound 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

Dapagliflozin

Renal impairment

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) may have mean systemic exposures of dapagliflozin that are 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment does not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion may be lower in patients with moderate or severe renal impairment compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion, may be highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day may be excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There may be no difference in the protein binding of dapagliflozin between renal impairment groups or compared to healthy patients. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin is contraindicated in patients whose GFR is less than 60 mL/min (see **section 4.3**).

Hepatic impairment

There may be no difference in the protein binding of dapagliflozin between hepatic impairment groups (Child-Pugh classes A, B and C) or compared to healthy patients. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin may be up to 12 % and 36 % higher, respectively, compared to healthy patients. These

differences may not be considered clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these patients. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin are up to 40 % and 67 % higher than in healthy patients, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see **section 4.4**).

Elderly

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The mean dapagliflozin systemic exposure (AUC) in young patients (≥ 18 to < 40 years) may be 10,4 % lower than in the ≥ 40 to < 65 years age group and 25 % higher in elderly patients (≥ 65 years) compared to the ≥ 40 to < 65 years age group. These differences in systemic exposure may not be considered clinically meaningful.

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

Paediatric and adolescent

No data are available regarding pharmacokinetics in paediatric and adolescent patients.

Special populations

Metformin

Renal impairment

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance may decrease in proportion to the decrease in creatinine clearance, leading to increased levels of metformin in plasma.

Elderly

The total plasma clearance of metformin in elderly patients may be decreased, the half-life prolonged and C_{max} increased compared to healthy young patients. The change in metformin pharmacokinetics with aging may be primarily accounted for by a change in renal function.

SYNGLUTRA should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is normal or only mildly impaired.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core

SYNGLUTRA 5/500 and SYNGLUTRA 5/1 000:

Carboxymethylcellulose sodium

Copovidone

Crospovidone

Ferric oxide red (E172)

Hypromellose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Silicon dioxide

SYNGLUTRA 10/500 and SYNGLUTRA 10/1 000

Carboxymethylcellulose sodium

Copovidone

Crospovidone

Ferric oxide yellow (E172)

Hypromellose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Silicon dioxide

Film-coating

SYNGLUTRA 5/500 Extended Release Tablets

Opadry II 85F17424 Beige film coating:

- Ferrosoferric oxide (E172)
- Iron oxide red (E172)
- Iron oxide yellow (E172)
- Macrogol (E1521)
- Part hydrolysed polyvinyl alcohol (E1203)
- Talc (E553b)
- Titanium dioxide (E171)

SYNGLUTRA 5/1 000 Extended Release Tablets

Opadry II 85F565267 Brown film coating:

- Iron oxide red (E172)
- Iron oxide yellow (E172)
- Macrogol (E1521)
- Part hydrolysed polyvinyl alcohol (E1203)
- Talc (E553b)
- Titanium dioxide (E171)

SYNGLUTRA 10/500 Extended Release Tablets

Opadry II 85F510122 Green film coating:

- FD&C Blue #2/Indigo carmine AL 3 % - 5 % (E132)
- Iron oxide yellow (E172)
- Macrogol (E1521)
- Part hydrolysed polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

SYNGLUTRA 10/1 000 Extended Release Tablets

Opadry II 85F94245 Pink film coating:

Iron oxide red (E172)

Macrogol (E1521)

Part hydrolysed polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

This medicine does not require any special storage conditions.

Store at or below 25 °C.

Keep bottle tightly closed.

Store in the original package.

6.5. Nature and contents of container

SYNGLUTRA 5/500: Packed in a 100 cc white HDPE container of 30 tablets with a 38 mm blue child-resistant cap and three 1 g silica gel bags.

SYNGLUTRA 5/1 000: Packed in a 100 cc white HDPE container of 30 tablets with a 38 mm

blue child-resistant cap and one 2 g silica gel bag

SYNGLUTRA 10/500: Packed in a 100 cc white HDPE container of 30 tablets with a 38 mm blue child-resistant cap and three 1 g silica gel bags

SYNGLUTRA 10/1 000: Packed in a 100 cc white HDPE container of 30 tablets with a 38 mm blue child-resistant cap and one 2 g silica gel bag.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

Mispel Street

Bellville

7530

RSA

Customer care number: 080 2226662

8. REGISTRATION NUMBER(S)

SYNGLUTRA 5/500: 53/21.2/0649

SYNGLUTRA 10/500: 53/21.2/0650

SYNGLUTRA 5/1 000: 53/21.1/0651

SYNGLUTRA 10/1 000: 53/21.1/0652

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 June 2021

10. DATE OF REVISION OF THE TEXT

Not applicable.