# SUMMARY OF PRODUCT CHARACTERISTICS

**DAPAGOOD SM 100 (Dapagliflozin 10 mg / Sitagliptin 100 mg / Metformin Hydrochloride 500 mg Extended-Release Bilayer Tablets)**

## 1. NAME OF THE MEDICINAL PRODUCT

DAPAGOOD SM 100 (Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin Hydrochloride 500 mg Extended-Release Tablets)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bilayer extended-release tablet contains:

- Dapagliflozin propanediol monohydrate equivalent to dapagliflozin 10 mg
- Sitagliptin phosphate monohydrate USP equivalent to sitagliptin 100 mg
- Metformin hydrochloride USP 500 mg (extended-release)

**Excipients with known effect:**

Each tablet contains 65 mg lactose monohydrate. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Extended-release bilayer tablet (uncoated).

Yellow and white coloured, caplet-shaped, bilayer uncoated tablet, scored on one side and plain on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DAPAGOOD SM 100 is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus who are inadequately controlled on their maximally tolerated dose of metformin, in combination with sitagliptin, or in patients already being treated with dapagliflozin, sitagliptin and metformin as separate tablets.

### 4.2 Posology and method of administration

**Adults**

One tablet once daily. The tablet should be taken with meals to reduce the gastrointestinal adverse reactions associated with metformin.

**Renal impairment**

Dapagliflozin: Do not initiate in patients with GFR <60 ml/min; discontinue if GFR falls persistently below 45 ml/min. Sitagliptin: A dose of 50 mg sitagliptin once daily is recommended for patients with moderate renal impairment (GFR 30–<45 ml/min); 25 mg once daily for severe renal impairment (GFR <30 ml/min) — DAPAGOOD SM 100 (containing 100 mg sitagliptin) should not be used in patients with GFR <45 ml/min (dose of sitagliptin needs reduction). Metformin: Contraindicated in patients with GFR <30 ml/min. This fixed-dose combination is not appropriate in moderate-to-severe renal impairment.

**Hepatic impairment**

Contraindicated in hepatic impairment due to the metformin component.

**Elderly**

Elderly patients are at greater risk of renal impairment, volume depletion and hypotension. Renal function should be monitored regularly before and during treatment.

**Paediatric population**

Safety and efficacy have not been established in patients below 18 years of age. Not recommended.

**Method of administration**

Oral. Swallow whole with water. Take with meals. Do not crush, cut or chew.

### 4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (GFR <30 ml/min).
- Acute conditions with potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents).
- Acute or chronic disease causing tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock).
- Hepatic impairment.
- Acute alcohol intoxication; alcoholism.
- Breast-feeding (see section 4.6).
- Patients with a history of serious hypersensitivity reactions to sitagliptin, such as anaphylaxis or angioedema.

## 4.4 Special warnings and precautions for use

**Lactic acidosis (metformin)**

Lactic acidosis, a very rare but serious and potentially fatal metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function. In case of dehydration (severe diarrhoea, vomiting, fever or reduced fluid intake), DAPAGOOD SM 100 should be temporarily discontinued. Medicinal products that can acutely impair renal function (antihypertensives, diuretics, NSAIDs) should be initiated with caution. Other risk factors include excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and hypoxia. Symptoms: acidotic dyspnoea, abdominal pain, muscle cramps, asthenia, hypothermia followed by coma. Diagnostic laboratory findings: pH <7.35, plasma lactate >5 mmol/L, increased anion gap and lactate/pyruvate ratio. If suspected, stop treatment immediately and seek emergency treatment.

**Renal function**

Assess renal function before initiation and regularly thereafter. For patients with GFR <60 ml/min and elderly patients, monitor at least 2–4 times per year. Discontinue DAPAGOOD SM 100 if GFR persistently falls below 45 ml/min. Acute conditions that may impair renal function require temporary discontinuation. Note also the sitagliptin dose restriction in moderate renal impairment (this fixed combination is not suitable in patients with GFR <45 ml/min).

**Diabetic ketoacidosis (DKA — dapagliflozin)**

Rare cases of DKA, including life-threatening and fatal cases, have been reported with SGLT2 inhibitors. In some cases, the presentation was atypical with only moderately elevated blood glucose (<14 mmol/L). The risk of DKA must be considered in the event of non-specific symptoms (nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness). If DKA is suspected or confirmed, discontinue immediately. Treatment should be interrupted in patients hospitalised for major surgical procedures or acute serious medical illness. Blood ketone levels should be monitored in these patients.

**Acute pancreatitis (sitagliptin)**

DPP-4 inhibitors have been associated with acute pancreatitis, including necrotising or haemorrhagic cases and deaths. Patients should be informed of the characteristic symptom: persistent, severe abdominal pain. If acute pancreatitis is suspected, DAPAGOOD SM 100 should be discontinued; if confirmed, it should not be restarted.

**Hypoglycaemia with insulin or sulfonylureas**

Concomitant use of DAPAGOOD SM 100 with insulin or insulin secretagogues (sulfonylureas) may increase the risk of hypoglycaemia. A lower dose of insulin or insulin secretagogue may be required.

**Volume depletion and hypotension (dapagliflozin)**

Dapagliflozin increases diuresis which may lead to a modest blood pressure decrease. This may be more pronounced in patients with high blood glucose concentrations. Use with caution in patients for whom a drop in blood pressure could pose a risk (patients on antihypertensive therapy, those with a history of hypotension, or elderly patients). Monitor for signs of volume depletion.

**Fournier's gangrene (dapagliflozin)**

Necrotising fasciitis of the perineum has been reported with SGLT2 inhibitors. This is rare but life-threatening. Seek medical attention if patients experience pain, tenderness, erythema or swelling in the genital or perineal area with fever or malaise. Discontinue DAPAGOOD SM 100 and institute prompt treatment (antibiotics, surgical debridement).

**Hypersensitivity reactions (sitagliptin)**

Post-marketing reports of serious hypersensitivity reactions with sitagliptin, including anaphylaxis, angioedema, SJS and bullous pemphigoid have been reported. If such reactions occur, discontinue DAPAGOOD SM 100 and seek prompt medical assessment.

**Surgery and iodinated contrast agents**

DAPAGOOD SM 100 must be discontinued at the time of surgery and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found stable. Iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactic acidosis; DAPAGOOD SM 100 must be discontinued prior to or at the time of the imaging procedure.

**Urine glucose and 1,5-AG assay**

Patients taking DAPAGOOD SM 100 will test positive for glucose in their urine. Monitoring glycaemic control with the 1,5-anhydroglucitol (1,5-AG) assay is not recommended in patients taking SGLT2 inhibitors.

**Lower limb amputations (dapagliflozin class)**

Routine preventative foot care should be counselled in all diabetic patients.

**Lactose content**

This product contains 65 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

See the individual component SmPCs for full details. Key interactions:

**Alcohol:**

Alcohol intoxication increases the risk of lactic acidosis (metformin). Avoid alcohol and alcohol-containing medicinal products.

**Iodinated contrast agents:**

See section 4.4.

**Cationic drugs eliminated by renal tubular secretion (e.g. cimetidine):**

May increase metformin exposure (AUC increased ~50%, Cmax ~81% with cimetidine); monitor glycaemic control.

**Diuretics (dapagliflozin):**

Additive diuretic effect; increased risk of dehydration and hypotension.

**Insulin and sulfonylureas:**

Increased risk of hypoglycaemia with dapagliflozin, metformin and sitagliptin; lower doses of insulin or sulfonylurea may be required.

**Drugs adversely affecting renal function (NSAIDs, ACE inhibitors, ARBs, loop diuretics):**

Close monitoring of renal function is necessary (lactic acidosis risk from metformin).

**Glucocorticoids, beta-2 agonists, diuretics (hyperglycaemic effect):**

Intensify blood glucose monitoring; adjust dose as necessary.

**UGT1A9 inhibitors (e.g. mefenamic acid) and inducers (e.g. rifampicin):**

May alter dapagliflozin exposure; no clinically meaningful effect on 24-hour urinary glucose excretion — no dose adjustment required.

Sitagliptin: No clinically meaningful pharmacokinetic interactions identified with warfarin, digoxin, metformin, glyburide, cyclosporine, rosiglitazone, atorvastatin, simvastatin, OCs, atenolol, amlodipine, felodipine, valsartan or pantoprazole.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

No adequate data on the use of DAPAGOOD SM 100 in pregnant women. Dapagliflozin: animal studies showed renal toxicity in the developing rat kidney during the period corresponding to the second and third trimesters of human pregnancy. Sitagliptin: animal reproductive toxicity observed at high doses; no adequate human data. Metformin: limited data do not indicate an increased risk of congenital malformations. Insulin is the preferred treatment for diabetes during pregnancy. DAPAGOOD SM 100 is not recommended during pregnancy.

**Breast-feeding**

Dapagliflozin/metabolites are excreted in animal milk and pharmacologically mediated effects in nursing offspring have been observed. Sitagliptin: excreted in rat milk. Metformin: excreted in human milk in small amounts. DAPAGOOD SM 100 is contraindicated during breast-feeding.

**Fertility**

No adverse effects on fertility have been observed for dapagliflozin, metformin or sitagliptin in animal studies.

### 4.7 Effects on ability to drive and use machines

DAPAGOOD SM 100 has no or negligible influence on the ability to drive and use machines. However, dizziness and somnolence have been reported with sitagliptin. Patients should be alerted to the risk of hypoglycaemia when DAPAGOOD SM 100 is used in combination with insulin or sulfonylureas.

### 4.8 Undesirable effects

**Summary of the safety profile**

The adverse reaction profile reflects those of the three individual components. The most common adverse reactions for the combination are gastrointestinal events (nausea, vomiting, diarrhoea, flatulence) — particularly with metformin at initiation. Dapagliflozin commonly causes genital mycotic infections and urinary tract infections. Sitagliptin commonly causes nasopharyngitis and upper respiratory tract infection.

| System Organ Class | Common (≥1/100 to <1/10) | Uncommon / Rare / Not known |
|---|---|---|
| Infections | Genital mycotic infections, UTI, nasopharyngitis, URTI | Pyelonephritis, urosepsis (uncommon); Fournier's gangrene (not known) |
| Metabolism | Hypoglycaemia (with SU/insulin); volume depletion | DKA (rare); lactic acidosis (metformin, very rare) |
| Nervous system | Headache, dizziness | Somnolence (uncommon) |
| Cardiac/vascular | | Hypotension/orthostatic hypotension (uncommon) |
| Respiratory | Cough (sitagliptin) | |
| Gastrointestinal | Nausea, vomiting, diarrhoea, flatulence, constipation (especially at initiation) | Pancreatitis (rare); lactic acidosis (metformin, very rare) |
| Skin | | Angioedema, urticaria, SJS, bullous pemphigoid (sitagliptin, rare/not known) |
| Musculoskeletal | Arthralgia (sitagliptin), back pain (dapagliflozin) | |
| Immune system | | Anaphylaxis, serious hypersensitivity (sitagliptin, not known) |
| Investigations | Increased serum creatinine/decreased eGFR (transient, dapagliflozin); increased haematocrit | Elevated liver enzymes (not known) |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

### 4.9 Overdose

**Dapagliflozin**

No toxicity at single oral doses up to 500 mg. In the event of overdose, appropriate supportive treatment should be initiated.

**Metformin**

High overdose or concomitant risks may lead to lactic acidosis — a medical emergency requiring hospital treatment. The most effective method to remove metformin and lactate is haemodialysis.

**Sitagliptin**

In event of overdose, institute general supportive measures. Sitagliptin is removed by haemodialysis. In clinical trials, single doses up to 800 mg were well tolerated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose-lowering drugs. ATC code: A10BD.

DAPAGOOD SM 100 combines three antihyperglycaemic agents with different and complementary mechanisms of action. Dapagliflozin (SGLT2 inhibitor): highly potent (Ki 0.55 nM), selective and reversible inhibitor of SGLT2 — the predominant transporter responsible for renal glucose reabsorption. Reduces renal glucose reabsorption leading to urinary glucose excretion of approximately 70 g/day at 10 mg in type 2 diabetes. Acts independently of insulin secretion and insulin action. Sitagliptin (DPP-4 inhibitor): highly selective inhibitor of DPP-4 enzyme that does not inhibit DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-4 increases active incretin hormones (GLP-1 and GIP), which increase insulin synthesis/release and lower glucagon secretion in a glucose-dependent manner. Metformin (biguanide): lowers both basal and postprandial plasma glucose without stimulating insulin secretion. Acts by: reducing hepatic glucose production (inhibiting gluconeogenesis and glycogenolysis); modestly improving insulin sensitivity; delaying intestinal glucose absorption.

### 5.2 Pharmacokinetic properties

DAPAGOOD SM 100 is considered bioequivalent to co-administered individual components. Dapagliflozin: Tmax approximately 2 hours (fasted); bioavailability 78%; protein binding 91%; volume of distribution 118 L; half-life 12.9 hours; metabolised primarily to dapagliflozin 3-O-glucuronide (inactive, via UGT1A9); 75% excreted in urine, 21% in faeces. Sitagliptin: Tmax 1–4 hours; bioavailability approximately 87%; volume of distribution approximately 198 L; protein binding approximately 38%; excreted approximately 79% unchanged in urine; renal clearance approximately 350 ml/min; half-life approximately 12.4 hours. Metformin: Tmax 2.5 hours; bioavailability 50–60%; plasma protein binding negligible; excreted unchanged in urine; renal clearance >400 ml/min; half-life approximately 6.5 hours.

### 5.3 Preclinical safety data

Dapagliflozin: No special hazard for humans based on conventional safety studies. Renal pelvic and tubular dilatations in rat progeny with exposure during late pregnancy/lactation. Metformin: No special hazard. Sitagliptin: Renal and liver toxicity at exposures 58 times human exposure (no-effect level 19-fold). Incisor teeth abnormalities in rats at 67-fold clinical exposure. Transient neurological signs in dogs at 23-fold exposure. Sitagliptin not genotoxic; not carcinogenic in mice; increased hepatic adenomas and carcinomas in rats at 58-fold exposure (considered secondary to hepatotoxicity and not clinically relevant given 19-fold no-effect level).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

| No. | Excipient | Specification |
|---|---|---|
| 1 | Hydroxypropyl methylcellulose (HPMC) | USP |
| 2 | Sodium carboxymethylcellulose (Sodium CMC) | USP |
| 3 | Povidone K-30 | USP |
| 4 | Isopropyl alcohol | USP |
| 5 | Magnesium stearate | USP |
| 6 | Microcrystalline cellulose (plain) | USP |
| 7 | Lactose monohydrate (excipient with known effect — 65 mg per tablet) | USP |
| 8 | Quinoline yellow lake (E104) | IH |
| 9 | Low-substituted hydroxypropylcellulose (LH-11) | USP |
| 10 | Crospovidone | USP |
| 11 | Colloidal silicon dioxide (Aerosil) | USP |

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life
36 months.

### 6.4 Special precautions for storage
Store below 30°C. Protect from light and moisture. Keep out of the reach and sight of children.

### 6.5 Nature and contents of container
10 tablets packed in one ALU-ALU blister; 3 such blisters packed in one carton with package insert. Pack size: 30 tablets.

### 6.6 Special precautions for disposal and other handling
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER
**ZAIN PHARMA LTD.**

Plot No. 209/13741, Colchester Park,

Go-Down No. 1, 2, 3, Off Mombasa Road,

Behind Nice and Lovely House,

P.O. Box: 100167-00101, Nairobi, Kenya.

## 8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)
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