ENCELIN D

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

abbreviated prescribing information for ENCELIN D (Dapagliflozin and Vildagliptin Sustained Release Tablets) [Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES: ***Dapagliflozin:*** is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2. ***Vildagliptin:*** The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

INDICATION: It is indicated for the treatment of patients with Type 2 Diabetes Mellitus inadequately controlled on Metformin monotherapy.

DOSAGE AND ADMINISTRATION: Encelin D 5 + 100 mg and 10 +100 mg Bilayer sustained release tablet, Should be taken as directed by Physician**.**

CONTRAINDICATION: ***Dapagliflozin and Vildagliptin***: Hypersensitivity to the active substance or to any of the excipients.

WARNINGS & PRECAUTIONS: ***Dapagliflozin:*** *Renal impairment*:There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2. *Hepatic impairment*: There is limited experience in clinical studies in patients with hepatic impairment. *Diabetic ketoacidosis*: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). *Urinary tract infections*: Urinary glucose excretion may be associated with an increased risk of urinary tract infection. *Cardiac failure:* Experience with dapagliflozin in NYHA class IV is limited. *Chronic kidney disease*: There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. *Lower limb amputations*: An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care. *Urine laboratory assessments*: Due to its mechanism of action, patients taking Forxiga will test positive for glucose in their urine. *Lactose:*The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ***Vildagliptin:*** Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. *Renal impairment:* There is limited experience in patients with ESRD on haemodialysis. *Hepatic impairment:* Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN. *Liver enzyme monitoring:* Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality (ies) return(s) to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of vildagliptin therapy is recommended. *Skin disorders:* Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies. Although skin lesions were not observed at an increased incidence

in clinical trials, there was limited experience in patients with diabetic skin complications. *Acute pancreatitis:*Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. *Hypoglycaemia:* Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

DRUG INTERACTIONS: ***Dapagliflozin:*** *Diuretics:* may increase the risk of dehydration and hypotension. *Insulin and insulin secretagogues:* such as sulphonylureas, cause hypoglycaemia Pharmacokinetic interactions: The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9). *Pharmacokinetics of dapagliflozin* are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant. Paediatric population Interaction studies have only been performed in adults. ***Vildagliptin:*** has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate and does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. *Combination with pioglitazone, metformin, glyburide, Digoxin, warfarin, amlodipine, Ramipril, valsartan or simvastatin: shown no clinically relevant pharmacokinetic interactions. ACE-inhibitors:* There may be an increased risk of angioedema in patients concomitantly taking ACE- inhibitors.

ADVERSE REACTIONS: ***Dapagliflozin:*** Angioedema, diabetic ketoacidosis, necrotising fasciitis of the perineum or Fournier's gangrene. Urinary tract infection, *Common:* genital infection, back pain, changes in the amount of cholesterol or fats in your blood, increases in the amount of red blood cells in your blood, decreases in creatinine renal clearance (shown in tests) dizziness, rash etc. *Uncommon:* dehydration, dry or sticky mouth, passing little or no urine or fast heartbeat, thirst, constipation, awakening from sleep at night to pass urine, weight decreased, increases in creatinine or increases in urea (shown in laboratory blood tests). ***Vildagliptin:*** Angioedema, Liver disease (hepatitis) (rare), Inflammation of the pancreas (pancreatitis) Some common side effects while taking Vildagliptin with Metformin, sulphonylurea, glitazone or insulin are Trembling, headache, dizziness, nausea, low blood glucose, Weight increase, swollen hands, ankle or feet (oedema), Dizziness, tremor, weakness, excessive sweating, Headache, chills, nausea (feeling sick), heartburn. Some common and rare side effects while taking Vildagliptin with Metformin, sulphonylurea, glitazone or insulin are Tiredness, Sore throat, runny nose, fever, Itchy rash, inflammation of the pancreas, localised peeling of skin or blisters, muscle pain, Constipation, Headache, weakness, low blood glucose, Headache, constipation, swollen hands, ankle or feet (oedema), joint pain, Diarrhoea and flatulence.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

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(Additional information is available on request)