For the use of a Registered Medical Practitioner Only

1. Generic Name and Brand Name:

Vildagliptin (As Sustained release) and Dapagliflozin Tablets 100 mg+10 mg

ABVIDA®-D

2. Qualitative and Quantitative Composition

Each uncoated bilayered tablet contains:
Vildagliptin I.P. ….100 mg
(As Sustained Release)
Dapagliflozin Propanediol Monohydrate I.P. equivalent to
Dapagliflozin….10 mg
Excipients …. q.s.
Colour: Ferric Oxide USP-NF (Yellow)

3. Dosage Form & Strength

Refer section 1 & 2

4. Clinical Particulars

4.1 Therapeutic Indication

Dapagliflozin and Vildagliptin Sustained Release tablets are indicated for the treatment of type 2 diabetes mellitus inadequately controlled on metformin monotherapy.

4.2 Posology and Method of Administration

Posology

The recommended dose is one tablet daily. Each tablet contains a fixed dose of dapagliflozin and Vildagliptin (As sustained Release).

Special populations

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), Vildagliptin SR is not recommended.

Hepatic impairment

This medicinal product must not be used in patients with hepatic impairment.

Elderly (≥ 65 years)

This medicinal product should be used with caution as age increases.

Paediatric population

The safety and efficacy of Dapagliflozin and Vildagliptin SR tablets have not yet been established. No data are available.

Method of administration

Dapagliflozin and Vildagliptin SR tablets should be given once daily.

4.3 Contraindications

Dapagliflozin and Vildagliptin SR tablets is contraindicated in patients with: hypersensitivity to the active substances or to any of the excipients used in the manufacturing of the finished product, any type of acute metabolic acidosis, diabetic pre-coma, severe renal failure, dehydration, severe infection, shock, cardiac or respiratory failure, acute alcohol intoxication and alcoholism.

4.4 Special Warnings and Precautions for Use

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. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 ml/min/1.73m2. The glucose lowering efficacy of dapagliflozin is dependent on renal function and is reduced in patients with eGFR < 45 ml/min/1.73m2 and is likely absent in patients with severe renal impairment. In patients with moderate renal impairment (eGFR < 60 ml/min/1. 73m2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.
- Hepatic impairment: There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.
- Volume depletion: Before initiating Dapagliflozin, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
- Ketoacidosis in Patients with Diabetes Mellitus: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue Dapagliflozin, evaluate and treat promptly. Before initiating Dapagliflozin, consider risk factors for ketoacidosis. Patients on Dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.
- Urosepsis and Pyelonephritis: Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Dapagliflozin.
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.
- Genital Mycotic Infections: Monitor and treat if indicated.

Vildagliptin

General

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

"No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), Vildagliptin 100 SR is not recommended."

Hepatic impairment

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN (see also sections 4.2 and 5.2).

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.
Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin.
Following withdrawal of treatment with Vildagliptin and LFT normalisation, treatment with Vildagliptin should not be reinitiated.

Cardiac failure

A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive (see section 5.1).
There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Furthermore, there have been post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended.

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.
If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history 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.

4.5 Drug Interactions

No interaction studies have been performed for Dapagliflozin and Vildaglitpin SR tablets. The following statements reflect the information available on the individual active substances.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, 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 in patients with type 2 diabetes mellitus.
In patients with type 1 diabetes mellitus and a known risk of frequent or severe hypoglycaemia, it may be necessary to reduce the insulin dose at the time of initiating treatment with Dapagliflozin to decrease the risk of hypoglycaemia. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Pharmacokinetic interactions

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

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

Vildagliptin

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.

Digoxin (Pgp substrate), warfarin (CYP2C9 substrate)

Clinical studies performed with healthy subjects have shown no clinically relevant pharmacokinetic interactions. However, this has not been established in the target population.

Combination with amlodipine, ramipril, valsartan or simvastatin

Drug-drug interaction studies in healthy subjects were conducted with amlodipine, ramipril, valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin.

Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors.

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

4.6 Use in Special Populations

Pregnancy

There are no data from the use of Dapagliflozin and Vildagliptin SR tablets or Dapagliflozin in pregnant women. There are no adequate data from the use of vildagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown.

Due to lack of human data, Vildagliptin should not be used during pregnancy.

Breast-feeding

It is unknown whether this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically mediated effects in nursing offspring. It is unknown whether vildagliptin is excreted in human milk. Animal studies have shown excretion of vildagliptin in milk. Vildagliptin should not be used during breast-feeding.

Fertility

The effect of this medicinal product or Dapagliflozin & Vildagliptin on fertility in humans has not been studied.

4.7 Effects on Ability to Drive and Use Machines

Dapagliflozin and Vildagliptin SR tablets have no or negligible influence on the ability to drive and use machines.

No studies on the effects of Vildagliptin (50mg) on the ability to drive and use machines have been performed. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines.

Patients should be alerted to the risk of hypoglycaemia when Dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable Effects

Dapagliflozin and Vildagliptin SR tablets have been demonstrated to be bioequivalent with co administered Dapagliflozin and Vildagliptin. There have been no therapeutic clinical trials conducted with Dapagliflozin and Vildagliptin SR tablets.

Tabulated list of adverse reactions for DAPAGLIFLOZIN

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia**		
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased	Blood creatinine increased during initial treatment[**,b]		

		during initial treatment[b] Dyslipidaemia[h]	Blood urea increased** Weight decreased**		

[a]The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b]See corresponding subsection below for additional information.

[c]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

[d]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[g]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus-0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

[h]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides –2.7% versus -0.7%.

[i]See section 4.4.

[j]Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.

[k]Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

*Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

**Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Summary of the safety profile for VILDAGLIPTIN

Safety data were obtained from a total of 3,784 patients exposed to vildagliptin at a daily dose of 50 mg (once daily) or 100 mg (50 mg twice daily or 100 mg once daily) in controlled trials of at least 12 weeks duration. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product. 2,682 patients were treated with vildagliptin 100 mg daily (either 50 mg twice daily or 100 mg once daily) and 1,102 patients were treated with vildagliptin 50 mg once daily.

The majority of adverse reactions in these trials were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Tabulated list of adverse reactions reported in patients who received Vildagliptin 100 mg daily as monotherapy in double-blind studies (N=1,855):

Infections and infestations	
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Nervous system disorders	
Common	Tremor
Common	Headache
Common	Dizziness
Common	Asthenia
Gastrointestinal disorders	
Uncommon	Constipation

Description of selected adverse reactions

In addition, in controlled monotherapy trials with vildagliptin the overall incidence of withdrawals due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.5%).
In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.
In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).
Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

4.9 Overdose
Dapagliflozin

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time {at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

Vildagliptin

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

5. Pharmacological Properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs.

5.1 Mechanism of Action

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action.

Urinary glucose excretion (glucuresis) induced by Dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by Dapagliflozin is also associated with mild diuresis and transient natriuresis.

The effect of vildagliptin layer 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).

5.2 Pharmacodynamic Properties

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2diabetes mellitus following the administration of dapagliflozin.

Vildagliptin

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin sustained release tablets 100 mg daily in patients with type 2

diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.
By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.
The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.
The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

5.3 Pharmacokinetic Properties

Dapagliflozin

Absorption: Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Geometric mean steady-state Dapagliflozin Cmax and AUCτ values following once daily 10 mg doses of Dapagliflozin were 158 ng/mL and 628 ng.h/mL, respectively. Maximum Dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increased proportionally to the increment in Dapagliflozin dose. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of Dapagliflozin in healthy subjects. Administration with a high-fat meal decreased Dapagliflozin Cmax by up to 50% and prolonged Tmax by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.
Distribution: Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.
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. The mean plasma terminal half-life (t1/2) for Dapagliflozin was 12.9 hours following a single oral dose of Dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-Dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 h]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of Dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.
Excretion: Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged Dapagliflozin. After administration of 50 mg [14C]-Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Vildagliptin

Pharmacokinetic Results:

The following pharmacokinetic parameters were calculated on data obtained from completed subjects for test and reference products.
Table 1: Summary of Pharmacokinetic Profile of Reference product (R) Dapagliflozin

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	23	166.9519±56.8111	34.0284	156.9640	106.1940	376.9450
AUC_{0-t} (ng.hr/mL)	23	659.4074±173.4975	26.3111	659.1434	430.7398	990.8904
$AUC_{0-\infty}$ (ng.hr/mL)	23	735.9804±260.2593	35.3623	687.0516	448.7871	1666.8857
t_{max} (hr)	23	1.5326±0.5074	33.1041	1.5000	0.7500	2.5000
K_{el} (1/hr)	23	0.1217±0.0645	52.9573	0.1115	0.0086	0.2757
$t_{1/2}$(hr)	23	10.0696±15.8330	157.2361	6.2100	2.5100	80.8200
$AUC_{\_\%Extrap\_obs}$	23	8.5970±8.4294	98.0510	5.7300	1.6000	41.1400

Table 2: Summary of Pharmacokinetic Profile of Test product (T) Dapagliflozin

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	23	155.5428±29.0509	18.6771	152.4210	90.4290	230.2100
AUC_{0-t} (ng.hr/mL)	23	670.0107±168.4710	25.1445	666.2883	433.1253	1080.9604
$AUC_{0-\infty}$ (ng.hr/mL)	23	723.2596±207.0085	28.6216	718.4159	446.0767	1331.9684
t_{max} (hr)	23	1.6630±0.7447	44.7800	1.5000	1.0000	4.5000
K_{el} (1/hr)	23	0.1247±0.0648	51.9871	0.1124	0.0177	0.2821
$t_{1/2}$(hr)	23	7.9191±7.3737	93.1129	6.1600	2.4600	39.2400
$AUC_{\_\%Extrap\_obs}$	23	6.6661±4.6401	69.6076	4.9800	1.6700	18.8400

Table 3: Statistical Results of Log Transformed Test product (T) versus Reference product (R) Dapagliflozin

Pharmacokinetic Parameter	Geometric Least		ISCV (%)	T/R Ratio	Power (%)	90% Confidence Interval
	Test	Reference				
C_{max} (ng/mL)	152.9264	160.3442	17.12	95.37	98.29	87.49 TO 103.97
AUC_{0-t} (ng.hr/mL)	651.9003	639.0446	9.16	102.01	100.0	97.38 TO 106.86
$AUC_{0-\infty}$ (ng.hr/mL)	699.6789	702.1710	14.14	99.65	99.73	92.77 TO 107.03

Table 4: Summary of Pharmacokinetic Profile of Reference product (R) Vildagliptin SR 100

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
Cmax (ng/mL)	23	235.4898±65.7523	27.9215	219.2450	159.9590	399.2770
AUC0-t (ng.hr/mL)	23	1504.9446±381.5313	25.3518	1437.1483	776.7608	2387.0285
AUC0-∞ (ng.hr/mL)	23	1605.6660±403.8884	25.1539	1528.3362	795.4177	2469.8166
tmax (hr)	23	4.4783±1.2834	28.6595	5.0000	1.0000	6.0000
Kel (1/hr)	23	0.1739±0.1029	59.1894	0.1696	0.0212	0.4193
t1/2(hr)	23	6.2348±6.3338	101.5889	4.0900	1.6500	32.7500
AUC_%Extrap_obs	23	6.1283±5.2859	86.2551	4.0000	0.7400	18.6600

Table 5: Summary of Pharmacokinetic Profile of Test product (T) Vildagliptin SR 100

Pharmacokinetic Parameter	N	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
Cmax (ng/mL)	23	247.8873±111.3208	44.9079	229.1580	115.3530	486.9860
AUC0-t (ng.hr/mL)	23	1686.0825±651.3056	38.6283	1649.7415	833.1419	3104.5396
AUC0-∞ (ng.hr/mL)	23	1775.8878±660.8700	37.2135	1709.3424	890.4177	3200.4050
tmax (hr)	23	4.7935±1.0517	21.9393	5.0000	1.7500	6.0000
Kel (1/hr)	23	0.1730±0.0823	47.5614	0.1493	0.0627	0.4113
t1/2(hr)	23	4.8374±2.1322	44.0780	4.6400	1.6900	11.0600
AUC_%Extrap_obs	23	5.5183±3.7712	68.3403	5.4600	0.7700	14.4200

Table 6: Statistical Results of Log Transformed Test product (T) versus Reference product (R) Vildagliptin SR 100

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)				
Cmax (ng/mL)	226.3107	228.2453	27.77	99.15	77.38	86.34 TO 113.87
AUC0-t (ng.hr/mL)	1574.1128	1460.1716	28.23	107.80	76.21	93.66 TO 124.08
AUC0-∞ (ng.hr/mL)	1667.4759	1557.4085	27.93	107.07	76.98	93.16 TO 123.06

6. Nonclinical Properties

6.1. Animal Toxicology or Pharmacology

Dapagliflozin:

In vivo primary pharmacodynamic studies with Dapagliflozin were carried out in single-dose, dose ranging studies in non-diabetic and diabetic rats or mice in order to evaluate the potency, SGLT2-specificity and duration of action in stimulating urinary glucose excretion, and to describe the secondary consequences of urinary glucose excretion, such as changes in urine volume or blood or plasma glucose effects. Subsequently a multiple-dose study was carried out to evaluate the ability of Dapagliflozin to have sustained effects on urinary glucose excretion, urine volume, and fasting plasma glucose in diabetic rats over a two-week dosing period.

Dapagliflozin increased renal glucose excretion in (healthy, non-diabetic) experimental animals. This was accompanied, by osmotic diuresis as measured by increased urine flow. An oral glucose tolerance test was also performed showing that Dapagliflozin was able to significantly reduce glucose area under the curve (AUC), compared to vehicle treatment. A study in knock-out mice lacking the gene for SGLT2 revealed that SGLT2 is indeed the main target for Dapagliflozin at least at lower doses. This study also demonstrated the reversibility of Dapagliflozin's action towards SGLT2.

Vildagliptin is a selective and potent inhibitor of DPP-4. The IC50 value for inhibition of human DPP-4 is about 3 nM and similar activity was observed with the rat enzyme, demonstrating the lack of species selectivity. Vildagliptin showed some activity at the related enzymes DPP-8 and DPP-9 (Ki values of 506 nM and 65 nM respectively). Although these values are 253 and 32 times higher than the Ki for DPP-4, activity at Cmax in humans (2.3 μM) is likely. No assays exist allowing evaluation of DPP-8/DPP-9 inhibition in vivo. The possibility of activity at one or both of these targets is considered a safety concern in relation to the occurrence of skin lesions in monkeys. No, or minimal, inhibition was seen with other related enzymes.

In vivo pharmacodynamic studies were performed in rats and monkeys. These studies demonstrated the in vivo inhibition of DPP-4 and increased plasma levels of GLP-1. Studies in diabetic rats and in insulin-resistant monkeys demonstrated a glucose-lowering effect of Vildagliptin. Chronic effects of Vildagliptin were studied in pre-diabetic and insulin-treated diabetic monkeys. Beneficial effects were observed on HbA1c, fasting insulin, fibrinogen and PAI-1.

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on Cmax). Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure based on ALIC) and in mice 750 mg/kg (142-fold human exposure). Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs.A no-effect level was not established. Vildagliptin was not mutagenic in conventional in vitro and in vivo tests for genotoxicity. A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development due to vildagliptin. Embryo-foetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced maternal body weight parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of developmental delays were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study was performed in rats. Findings were only observed in association with maternal toxicity at ~ 150 mg/kg and included a transient decrease in body weight and reduced motor activity in the F1 generation. A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose}. No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure} and 100 mg/kg (16-fold human exposure}, respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans based on the lack of genotoxicity of vildagliptin and its principal metabolite, the occurrence of tumours only in one species and the high systemic exposure ratios at which tumours were observed. In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses~ 5 mg/kg/day. These were consistently located on the extremities (hands, feet, ears and tail}. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose}, only blisters were observed. They were reversible despite continued treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were noted at doses.!: 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose}. Necrotic lesions of the tail were observed at ~ 80 mg/kg/day. Skin lesions were not reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

6.2.Clinical Studies

A phase III, prospective, randomized, double blind, active-controlled, comparative, parallel group, multicentric clinical study was conducted on 270 patients. The outcome of the study is as follows:

Efficacy Results:

Fixed dose combination therapy of Dapagliflozin 5 mg / 10 mg + Vildagliptin SR 100 mg / 100 mg Tablets were produced statistically significant reductions in HbA1c, fasting plasma glucose & 2-hour post prandial glucose.

Safety Results:

For evaluation of safety, frequency of suspected, unanticipated adverse drug reactions reported possibly related to the investigational product up to end of study from start of the treatment was considered. Safety and tolerability of the test and reference products were assessed depending on the outcome from this clinical study. There were events and evidence of adverse reaction observed but was non-significant. Total 64 AEs were reported in 64 patients. 18 AEs were reported in FDC of Dapagliflozin 5 mg + Vildagliptin SR 100 mg Tablets arm, 25 AEs were reported in FDC of Dapagliflozin 10 mg + Vildagliptin SR 100 mg Tablets arm and 21

AEs were reported in FDC of Dapagliflozin 10 mg + Saxagliptin 5 mg Tablets arm. No SAE was reported during the study.
Conclusion: FDC of Dapagliflozin 5 mg + Vildagliptin SR 100 mg Tablets and FDC of Dapagliflozin 10 mg + Vildagliptin SR 100 mg Tablets was non-inferior to FDC of Dapagliflozin 10 mg + Saxagliptin 5 mg Tablets. There were no deaths or hospitalizations in all the three treatment groups. FDC of Dapagliflozin 5 mg + Vildagliptin SR 100 mg Tablets and FDC of Dapagliflozin 10 mg + Vildagliptin SR 100 mg Tablets were found to be safe and well tolerated in patients with type 2 diabetes mellitus.

7. Description
Abvida D is supplied for oral administration, as an uncoated bilayered tablet of Vildagliptin & Dapagliflozin Propanediol. Each uncoated bilayered tablet of Abvida D contains Vildagliptin (As Sustained Release) 100mg & Dapagliflozin Propanediol equivalent to Dapagliflozin 10 mg.

8. Pharmaceutical Particulars
8.1.Incompatibilities
Not applicable.

8.2.Shelf- Life
Refer Pack

8.3.Packaging Information
Refer Pack

8.4.Storage And Handing Instructions
Refer Pack

9. Patient Counseling Information
What is Dapagliflozin and Vildagliptin Sustained Release Tablets?
The both active substances of these combinations belong to a group of medicines called “oral antidiabetics”.
Vildagliptin Layer: Vildagliptin is used to treat adult patients with type 2 diabetes. It is used when diabetes cannot be controlled by diet and exercise alone. It helps to control the level of sugar in the blood. Your doctor will prescribe Vildagliptin either alone or together with certain other antidiabetic medicines which you will already be taking, if these have not proved sufficiently effective to control diabetes. Type 2 diabetes develops if the body does not make enough insulin or if the insulin that the body makes does not work as well as it should. It can also develop if the body produces too much glucagon.
Insulin is a substance which helps to lower the level of sugar in the blood, especially after meals. Glucagon is a substance with triggers the production of sugar by the liver, causing the blood sugar level to rise. The pancreas makes both of these substances.
Dapagliflozin Layer: Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).
SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production

in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action.
Urinary glucose excretion (glucuresis) induced by Dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by Dapagliflozin is also associated with mild diuresis and transient natriuresis.

Do not take Dapagliflozin and Vildagliptin Sustained Release Tablets:

if you are allergic to Dapagliflozin and Vildagliptin or any of the other ingredients of this medicine. If you think you may be allergic to Vildagliptin/Dapagliflozin or any of the other ingredients of Vildagliptin/Dapagliflozin, do not take this medicine and talk to your doctor.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Vildagliptin.

- if you have type 1 diabetes (i.e. your body does not produce insulin) or if you have a condition called diabetic ketoacidosis.
- if you are taking an anti-diabetic medicine known as sulphonylurea (your doctor may want to reduce your dose of the sulphonylurea when you take it together with Vildagliptin in order to avoid low blood glucose [hypoglycaemia]).
- if you have moderate or severe kidney disease (you will need to take a lower dose of this combination).
- if you are on dialysis.
- if you have liver disease.
- if you suffer from heart failure.
- if you have or have had a disease of the pancreas.

If you have previously taken Vildagliptin & Dapagliflozin individual components but had stopped taking it because of liver disease, you should not take this combination.
Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking Vildagliptin. Should these occur, you should promptly consult your doctor.
A test to determine your liver function will be performed before the start of Vildagliptin treatment, at three-month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible.

Children and adolescents

The use of this combination product in children and adolescents up to 18 years of age is not recommended.

Other medicines and Dapagliflozin and Vildagliptin Sustained Release Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may wish to alter your dose of Vildagliptin if you are taking other medicines such as:

- Thiazides or other diuretics (also called water tablets)
- Corticosteroid (generally used to treat inflammation)
- Thyroid medicines
- Certain medicines affecting the nervous system.

Pregnancy, breast feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

If you feel dizzy while taking this medicine, do not drive or use machines.

How will I receive Dapagliflozin and Vildagliptin Sustained Release Tablets?

Swallow the tablets whole with some water.

If you take more Dapagliflozin and Vildagliptin Sustained Release Tablets than you should

If you have taken too many tablets, contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take Dapagliflozin and Vildagliptin Sustained Release Tablets

If you miss a dose of Dapagliflozin and Vildagliptin Sustained Release Tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.

What are the possible side effects of Dapagliflozin and Vildagliptin Sustained Release Tablets?

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Stop taking this medicine and consult your doctor immediately if any of the following occur – you may need medical treatment.
Diabetic skin lesions are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse. You are also advised to pay particular attention to new onset of blisters or ulcers while taking this combination. Should these occur, you should promptly consult your doctor.

10. Details of Manufacturer

Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg.D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First floor,201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi- 421 302, Maharashtra, India.

11. Details of Permission or License Number

Refer pack for Permission/License details.

12. Date of Revision

Version No.5.0, dated 10-Jun-26

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**