To be sold by retail on the prescription of a R.M.P. only

EUREPA-V
(REPAGLINIDE AND VOGLIBOSE TABLETS)

1. **Generic Name**
   Repaglinide and Voglibose Tablets

2. **Qualitative and quantitative composition**

   Eurepa-V 0.5/0.2
   Each uncoated tablet contains:
   Repaglinide I.P. …..0.5mg
   Voglibose I.P……0.2mg

   The excipients used are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone and Magnesium Stearate.

   Eurepa-V 0.5/0.3
   Each uncoated tablet contains:
   Repaglinide I.P. …..0.5mg
   Voglibose I.P……0.3mg
   Colours: Red oxide of Iron & Yellow oxide of Iron

   The excipients used are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate, Red oxide of Iron and Yellow oxide of Iron.

   Eurepa-V 1/0.2
   Each uncoated tablet contains:
   Repaglinide I.P. …..1mg
   Voglibose I.P……0.2mg
   Colour: Yellow oxide of Iron

   The excipients used are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate and Yellow oxide of Iron.

   Eurepa-V 1/0.3
   Each uncoated tablet contains:
   Repaglinide I.P. …..1mg
   Voglibose I.P……0.3mg
   Colour: Red oxide of Iron

   The excipients used are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate and Red oxide of Iron.

3. **Dosage form and strength**
   Dosage Form: Uncoated Tablets
   Strength: 0.5mg+0.2mg, 1 mg+0.2 mg, 0.5mg+0.3mg and 1mg+0.3mg.

4. Clinical particulars

4.1 Therapeutic indication

Indicated for Type 2 Diabetes Mellitus as an adjunct to diet and exercise to improve glycemic control.

4.2 Posology and method of administration

Eurepa-V is to be taken preprandially. Dose is titrated individually to optimise glycaemic control. The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Starting Dose

For patients not previously treated or whose HbA1c is < 8%, the starting dose can be Repaglinide 0.5mg + Voglibose 0.2 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA1c is > 8%, the initial dose can be Repaglinide 1mg +Voglibose 0.3mg with each meal preprandially.

Dose Adjustment

Dosing adjustments, based on assessment of response after at least one week, should be determined by blood glucose response. Postprandial glucose levels testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA1c) is inadequate.

Eurepa-V may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient’s meal pattern.

Special populations

Elderly

Since elderly patients generally have a physiological hypo function, it is desirable that such caution be taken as, starting the administration at a low dose. Furthermore, this drug should be carefully administered under close observation, through the course of the disease condition, with careful attention to the blood sugar level and the onset of gastrointestinal symptoms.

Renal impairment

Single-dose and steady-state pharmacokinetics of Repaglinide were compared between patients with type 2 diabetes and normal renal function (CrCl > 80 mL/min), mild to moderate renal function impairment (CrCl = 40 – 80 mL/min), and severe renal function impairment (CrCl = 20 – 40 mL/min). Both AUC and Cmax of Repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/mL*hr vs 57.2 ng/mL*hr and 37.5 ng/mL vs 37.7 ng/mL, respectively). Patients with severely reduced renal function had elevated mean AUC and Cmax values (98.0 ng/mL*hr and 50.7 ng/mL, respectively), but this study showed only a weak correlation between Repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. However, patients with type 2 diabetes who have severe renal function impairment should initiate therapy with the 0.5 mg dose – subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 mL/min or patients with renal failure requiring hemodialysis.

Voglibose is excreted rapidly in stools and has only negligible renal excretion. As Voglibose has no active metabolites and only negligible renal excretion, it is suitable for use in patients on hemodialysis.

Pharmacokinetic studies in patients with renal insufficiency have not been carried out.

Hepatic impairment
A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound Repaglinide than healthy subjects (AUChealthy: 91.6 ng/mL*hr; AUCCLD patients: 368.9 ng/mL*hr; Cmax, healthy: 46.7 ng/mL; Cmax, CLD patients: 105.4 ng/mL). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of Repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, the Eurepa-V should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.

After ingestion of Voglibose, the majority of active unchanged drug remains in the lumen of the gastrointestinal tract, where it is metabolized by intestinal enzymes and microbial flora. No active metabolites have been identified to date.

Debilitated or malnourished patients
In debilitated or malnourished patients, the initial and maintenance dosage should be conservative and careful dose titration is required to avoid hypoglycaemic reactions.

Paediatric population
The safety and efficacy of Eurepa-V in children below 18 years have not been established.

Method of administration
Eurepa-V should be taken before main meals (i.e. preprandially).

Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal (i.e. preprandially 2, 3, or 4 meals a day). Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.

In the case of concomitant use with other active substances refer to sections 4.4 and 4.5 to assess the dosage.

4.3 Contraindications

- Hypersensitivity to active substances or to any of the excipients of this product
- Diabetes mellitus type 1, C-peptide negative
- Diabetic ketoacidosis, with or without coma
- Severe hepatic function disorder
- Concomitant use of gemfibrozil (see section 4.5)
- Severe infection, before and after operation or with serious trauma
- Gastrointestinal obstruction or predisposition to it

4.4 Special warnings and precautions for use

General

The administration of Eurepa-V should be limited to patients who have established diabetes, as there are certain other disease conditions such as abnormal glucose tolerance and positive urinary sugar that represent diabetes-like symptoms (renal glycosuria, senile abnormal glucose tolerance, abnormal thyroid function, etc).

Eurepa-V Tablets should only be prescribed if poor blood glucose control and symptoms of diabetes persist despite adequate attempts at dieting, exercise and weight reduction.

When a patient stabilised on any oral hypoglycaemic medicinal product is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control may occur. At such times, it may be necessary to discontinue the therapy and treat with insulin on a temporary basis.

Hypoglycaemia

Repaglinide, like other insulin secretagogues, is capable of producing hypoglycaemia. Though the frequency of hypoglycaemia reported with Eurepa-V combination was less than that reported with Repaglinide alone.

Combination with insulin secretagogues

The blood glucose-lowering effect of oral hypoglycaemic medicinal products decreases in many patients over time. This may be due to progression of the severity of the diabetes or to diminished responsiveness to the medicinal product. This phenomenon is known as secondary failure, to distinguish it from primary failure, where the medicinal product is ineffective in an individual patient when first given. Adjustment of dose and adherence to diet and exercise should be assessed before classifying a patient as a secondary failure.

Repaglinide acts through a distinct binding site with a short action on the β-cells. Use of Repaglinide in case of secondary failure to insulin secretagogues has not been investigated in clinical trials. Trials investigating the combination with other insulin secretagogues have not been performed.

Combination with Neutral Protamine Hagedorn (NPH) insulin or thiazolidinediones

As per reported data, trials of combination therapy with NPH insulin or thiazolidinediones have been performed. However, the benefit risk profile remains to be established when comparing to other combination therapies.

Combination with metformin

Combination treatment with metformin is associated with an increased risk of hypoglycaemia. Though the frequency of hypoglycaemia reported with Eurepa-V was less than that reported with Repaglinide alone.

Acute coronary syndrome

The use of Repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction).

Concomitant use

Repaglinide should be used with caution or be avoided in patients receiving medicinal products which influence Repaglinide and Voglibose metabolism. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

Voglibose tablets should be administered with caution to the following patients:

- Patients with history of laparotomy or ileus

- Patients with chronic intestinal disease accompanied by disturbance in digestion and absorption
- Patients with aggravating symptoms due to increased generation of intestinal gas (eg, roemheld syndrome, severe hernia, and stenosis and ulcer of the large intestine)
- Patients with serious hepatic or renal disorders

Other Precautions:

- All patients should continue their dietary restriction with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Patients should be instructed and explained to recognize hypoglycemic symptoms and its management.

4.5 Drugs interactions

Repaglinide

A number of medicinal products are known to influence Repaglinide metabolism. Possible interactions should therefore be taken into account by the physician.

Reported *in vitro* data indicate that Repaglinide is metabolised predominantly by CYP2C8, but also by CYP3A4. Reported clinical data in healthy volunteers support CYP2C8 as being the most important enzyme involved in Repaglinide metabolism with CYP3A4 playing a minor role, but the relative contribution of CYP3A4 can be increased if CYP2C8 is inhibited. Consequently metabolism, and by that clearance of Repaglinide, may be altered by substances which influence these cytochrome P-450 enzymes via inhibition or induction. Special care should be taken when inhibitors of both CYP2C8 and 3A4 are co-administered simultaneously with Repaglinide.

Based on reported *in vitro* data, Repaglinide appears to be a substrate for active hepatic uptake (organic anion transporting protein OATP1B1). Substances that inhibit OATP1B1 may likewise have the potential to increase plasma concentrations of Repaglinide, as has been shown for ciclosporin (see below).

The following substances may enhance and/or prolong the hypoglycaemic effect of Repaglinide: Gemfibrozil, clarithromycin, itraconazole, ketokonazole, trimethoprim, ciclosporin, deferasirox, clopidogrel, other antidiabetic substances, monoamine oxidase inhibitors (MAOI), non selective beta blocking substances, angiotensin converting enzyme (ACE)-inhibitors, salicylates, NSAIDs, octreotide, alcohol, and anabolic steroids.

Co-administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and Repaglinide (a single dose of 0.25 mg) increased the Repaglinide AUC 8.1-fold and C_{max} 2.4-fold in healthy volunteers. Half-life was prolonged from 1.3 hr to 3.7 hr, resulting in possibly enhanced and prolonged blood glucose-lowering effect of Repaglinide, and plasma Repaglinide concentration at 7 hr was increased 28.6-fold by gemfibrozil. The concomitant use of gemfibrozil and Repaglinide is contraindicated.

Co-administration of trimethoprim (160 mg twice daily), a moderate CYP2C8 inhibitor, and Repaglinide (a single dose of 0.25 mg) increased the Repaglinide AUC, C_{max} and $t_{½}$ (1.6-fold, 1.4-fold and 1.2-fold respectively) with no statistically significant effects on the blood glucose levels. This lack of pharmacodynamic effect was observed with a sub-therapeutic dose of Repaglinide. Since the safety profile of this combination has not

been established with dosages higher than 0.25 mg for Repaglinide and 320 mg for trimethoprim, the concomitant use of trimethoprim with Repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

Rifampicin, a potent inducer of CYP3A4, but also CYP2C8, acts both as an inducer and inhibitor of the metabolism of Repaglinide. As per reported data, Seven days pre-treatment with rifampicin (600 mg), followed by co-administration of Repaglinide (a single dose of 4 mg) at day seven resulted in a 50% lower AUC (effect of a combined induction and inhibition). When Repaglinide was given 24 hours after the last rifampicin dose, an 80% reduction of the Repaglinide AUC was observed (effect of induction alone).

Concomitant use of rifampicin and Repaglinide might therefore induce a need for Repaglinide dose adjustment which should be based on carefully monitored blood glucose concentrations at both initiation of rifampicin treatment (acute inhibition), following dosing (mixed inhibition and induction), withdrawal (induction alone) and up to approximately two weeks after withdrawal of rifampicin where the inductive effect of rifampicin is no longer present. It cannot be excluded that other inducers, e.g. phenytoin, carbamazepine, phenobarbital, St John's wort, may have a similar effect.

As per reported data, the effect of ketoconazole, a prototype of potent and competitive inhibitors of CYP3A4, on the pharmacokinetics of Repaglinide has been studied in healthy subjects. Co-administration of 200 mg ketoconazole increased the Repaglinide (AUC and C_{max}) by 1.2-fold with profiles of blood glucose concentrations altered by less than 8% when administered concomitantly (a single dose of 4 mg Repaglinide). Co-administration of 100 mg itraconazole, an inhibitor of CYP3A4, has also been studied in healthy volunteers, and increased the AUC by 1.4-fold. No significant effect on the glucose level in healthy volunteers was observed. In a reported interaction study in healthy volunteers, co-administration of 250 mg clarithromycin, a potent mechanism-based inhibitor of CYP3A4, slightly increased the Repaglinide (AUC) by 1.4-fold and C_{max} by 1.7-fold and increased the mean incremental AUC of serum insulin by 1.5-fold and the maximum concentration by 1.6-fold. The exact mechanism of this interaction is not clear.

In a reported study conducted in healthy volunteers, the concomitant administration of Repaglinide and ciclosporin (repeated dose at 100 mg) increased Repaglinide AUC and C_{max} about 2.5-fold and 1.8-fold respectively. Since the interaction has not been established with dosages higher than 0.25 mg for Repaglinide, the concomitant use of ciclosporin with Repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed.

In a reported interaction study with healthy volunteers, co-administration of deferasirox (30 mg/kg/day, 4 days), a moderate inhibitor of CYP2C8 and CYP3A4, and Repaglinide (single dose, 0.5 mg) resulted in an increase in Repaglinide systemic exposure (AUC) to 2.3-fold (90% CI [2.03-2.63]) of control, a 1.6-fold (90% CI [1.42-1.84]) increase in C_{max}, and a small, significant decrease in blood glucose values. Since the interaction has not been established with dosages higher than 0.5 mg for Repaglinide, the concomitant use of deferasirox with Repaglinide should be avoided. If the combination appears necessary, careful clinical and blood glucose monitoring should be performed.

In a reported interaction study with healthy volunteers, co-administration of *clopidogrel* (300 mg loading dose), a CYP2C8 inhibitor, increased Repaglinide

exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased Repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment has not been established in these patients, the concomitant use of clopidogrel and Repaglinide should be avoided. If concomitant use is necessary, careful monitoring of blood glucose and close clinical monitoring should be performed.

β-blocking medicinal products may mask the symptoms of hypoglycaemia.

Co-administration of cimetidine, nifedipine, oestrogen, or simvastatin with Repaglinide, all CYP3A4 substrates, did not significantly alter the pharmacokinetic parameters of Repaglinide.

Repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline or warfarin at steady state, when administered to healthy volunteers. Dosage adjustment of these compounds when co-administered with Repaglinide is therefore not necessary.

The following substances may reduce the hypoglycaemic effect of Repaglinide:

Oral contraceptives, rifampicin, barbiturates, carbamazepine, thiazides, corticosteroids, danazol, thyroid hormones and sympathomimetics.

When these medications are administered to or withdrawn from a patient receiving Repaglinide, the patient should be observed closely for changes in glycaemic control.

When Repaglinide is used together with other medicinal products that are mainly secreted by the bile, like Repaglinide, any potential interaction should be considered.

Paediatric population

No interaction studies have been performed in children and adolescents.

Voglibose

When Voglibose is used in combination with derivative(s) of sulfonylamide, sulfonylurea or biguanide, or with insulin, hypoglycemic symptoms may occur. Therefore, when used in combination with any of these drugs, care should be taken, such as starting the administration at a low dose. Though the frequency of hypoglycaemia reported with Repaglinide and Voglibose combination with metformin was less than that reported with Repaglinide alone.

When Voglibose is administered concomitantly with drugs that enhance or diminish the hypoglycemic action of antidiabetic drugs, caution should be taken as this might additionally delay the action of Voglibose on the absorption of carbohydrates. Examples of drugs enhancing the hypoglycemic action of antidiabetic drugs: α-blockers, salicylic acid preparations, monoamine oxidase inhibitors, and fibrate derivatives. Examples of drugs diminishing the hypoglycemic action of antidiabetic drugs: epinephrine, adrenocortical hormone, and thyroid hormone.

Voglibose does not affect the pharmacokinetics of warfarin; hence it can be safely administered along with warfarin.

4.6 Use in special populations (such as pregnant women, lactating women, paediatricpatients, geriatric patients etc.)

Pregnancy

To date, no relevant epidemiological data are available. Reported animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or post natal development, therefore the drug should be given to pregnant women or women suspected of being pregnant only when the potential benefits outweigh the possible hazards.

Breast-feeding

Reported animal studies (rats) have revealed a suppressive action of Voglibose on body weight increase in new-borns presumably due to suppression of milk production in mother animals resulting from suppression of carbohydrate absorption. Therefore, it is desirable not to give Eurepa-V to women during lactation. When the administration is unavoidable, nursing should be avoided.

4.7 Effects on ability to drive and use machines

Eurepa-V have no direct influence on the ability to drive and use machines but may cause hypoglycaemia.

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile (from published reports)

The most frequently reported adverse reactions are changes in blood glucose levels, i.e. hypoglycaemia. The occurrence of such reactions depends on individual factors, such as dietary habits, dosage, exercise and stress.

Tabulated list of adverse reactions

Based on the experience with Repaglinide and with other hypoglycaemic medicinal products the following adverse reactions have been seen: Frequencies are defined as: 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).

Immune system disorders	Allergic reactions*	Very rare
	Face oedema	Not Known
Metabolism and nutrition disorders	Hypoglycaemia	Common
	Hypoglycaemic coma and hypoglycaemic unconsciousness, hyperkalemia	Not known
Eye disorders	Refraction disorder*, blurred vision	Very rare
Cardiac disorders	Cardiovascular disease	Rare
	Abdominal pain, diarrhea	Common

Gastrointestinal disorders	Vomiting, constipation	Very rare
	Nausea, loose stools, anorexia, heartburn, abdominal distension, increased flatus, intestinal obstruction like symptoms (due to increased intestinal gas)	Not known
Hepatobiliary disorders	Abnormal hepatic function, increased liver enzymes*, hyperammonemia*	Very rare
Skin and subcutaneous tissue disorders	Hypersensitivity*, diaphoresis, alopecia	Not known
Hematologic disorders	Anemia; thrombocytopenia, and leucopenia	Rare
Nervous System Disorders	Headache	Rare
	Numbness	Not Known
General disorders and administration site conditions	Hot Flushes, malaise, weakness,	Not Known

* see section 'Description of selected adverse reactions' below

Description of selected adverse reactions

Allergic reactions
Generalised hypersensitivity reactions (e.g. anaphylactic reaction), or immunological reactions such as vasculitis.

Refraction disorders
Changes in blood glucose levels have been known to result in transient visual disturbances, especially at the commencement of treatment. Such disturbances have only been reported in very few cases after initiation of Repaglinide treatment. No such cases have led to discontinuation of Repaglinide treatment in reported clinical trials.

Abnormal hepatic function, increased liver enzymes
Isolated cases of increased liver enzymes have been reported during treatment with Repaglinide. Most cases were mild and transient, and very few patients discontinued treatment due to increased liver enzymes. In very rare cases, severe hepatic dysfunction has been reported.

Hypersensitivity
Hypersensitivity reactions of the skin may occur as erythema, itching, rashes, pruritus and urticaria. In such a case, Eurepa-V should be discontinued. There is no reason to suspect cross-allergenicity with sulphonylurea due to the difference in chemical structure.

Hyperammonemia
When Voglibose is administered to patients with serious liver cirrhosis, hyperammonia may worsen with the development of constipation followed by disturbance of consciousness.

Data from other reported studies

As per reported data, in type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of Repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not

persist beyond the time of the meal challenge. Plasma Repaglinide levels decreased rapidly, and low concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration.

As per reported data, a dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg Repaglinide.

Reported clinical study results have shown that Repaglinide is optimally dosed in relation to main meals (preprandial dosing).

Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

One reported epidemiological study suggested an increased risk of acute coronary syndrome in Repaglinide treated patients as compared to sulfonylurea treated patients.

In a reported randomized double-blind trial comprising 1780 Japanese individuals with impaired glucose tolerance, who were treated for an average of 48.1 weeks (standard deviation, SD=36.3), Ryuzo Kawamori et al reported Voglibose to be better than placebo (p=0.0026). It was noted that Voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance.

Kazuhisa Takami et al examined the effects of dietary modification/restriction alone and dietary modification/restriction with Voglibose or glyburide on abdominal adiposity and metabolic abnormalities in 36 Japanese patients with type 2 diabetes. In newly diagnosed patients who were relatively lean but had excess visceral adipose tissue area (VAT), dietary modification/restriction (with or without Voglibose or glyburide) effectively reduced VAT. Decrease in VAT was closely associated with improvement of glycemic control through diet. Additional use of Voglibose or low dose glyburide had no detrimental effects on abdominal adiposity and had beneficial effects on insulin sensitivity and the acute insulin response.

In another reported trial, treatment with Voglibose in diabetes mellitus patients demonstrated improved post prandial blood glucose levels, a significant decline of triglyceride level, and an elevation of high density lipoprotein (HDL) cholesterol and apolipoprotein A-1. As compared to acarbose, Voglibose was more effective and had fewer side effects.

In a reported meta analysis comparing miglitol and Voglibose, nosignificant differences in post prandial glucose were observed between the 2 groups.

Safety Evaluation (Phase 3 clinical trial in Indian patients)

Frequency of Hypoglycaemic episodes

Summary of hypoglycemic events at different visit in safety population is presented in below table

Summary of Hypoglycemic Events at different Visit-Safety Population (N=206)

Week	Repaglinide+Voglibose (N=103)	Repaglinide (N=103)
Week-2	2 (1.9%)	0 (0.0%)
Week-3	1 (1.0%)	0 (0.0%)
Week-4	0 (0.0%)	2 (1.9%)

Week-5	1 (1.0%)	1 (1.0%)
Week-7	2 (1.9%)	2 (1.9%)
Week-8	2 (1.9%)	3 (2.9%)
Week-10	1 (1.0%)	1 (1.0%)
Week-11	2 (1.9%)	1 (1.0%)
Week-12	2 (1.9%)	3 (2.9%)
Week-9	1 (1.0%)	1 (1.0%)
Week-13	1 (1.0%)	0 (0.0%)
Week-14	0 (0.0%)	2 (1.9%)
Week-15	2 (1.9%)	2 (1.9%)
Week-16	2 (1.9%)	1 (1.0%)
Week-18	1 (1.0%)	0 (0.0%)
Week-19	0 (0.0%)	3 (2.9%)
Week-20	3 (2.9%)	0 (0.0%)
Week-21	0 (0.0%)	2 (1.9%)
Week-22	0 (0.0%)	3 (2.9%)
Week-23	0 (0.0%)	1 (1.0%)
Week-24	0 (0.0%)	1 (1.0%)
Note: Percentages were calculated using respective column header count as denominator		

Adverse Events

Summary of Adverse Events by System Organ Class (SOC) and Preferred Term (PT) by Treatment Group in Safety Population is tabulated in Table 2. A total of 44 AEs were recorded in 34 (16.5%) subjects. The AEs has been described under following SOC and PT.

In the **Repaglinide+Voglibose** (RV) as well **Repaglinide** (R) arms, none of the subjects presented serious adverse events during the study.

Summary of Adverse Events by System Organ Class (SOC) and Preferred Term (PT) by Treatment Group- Safety Population (N=206)

		Repaglinide+ Voglibose (N=103)	**Repaglinide (N=103)**	**Overall (N=206)**
System Organ Class	**Preferred Term**			
TOTAL (ALL SOC/PT)	NA	15(14.6%)	19(18.4%)	34(16.5%)
		0(0.0%)	1(1.0%)	1(0.5%)

Blood and lymphatic system disorders	Anaemia	0(0.0%)	1(1.0%)	1(0.5%)
Gastrointestinal disorders		5(4.9%)	9(8.7%)	14(6.8%)
	Abdominal discomfort	0(0.0%)	1(1.0%)	1(0.5%)
	Abdominal distension	1(1.0%)	0(0.0%)	1(0.5%)
	Abdominal pain upper	0(0.0%)	1(1.0%)	1(0.5%)
	Diarrhoea	3(2.9%)	1(1.0%)	4(1.9%)
	Gastritis	1(1.0%)	2(1.9%)	3(1.5%)
	Hyperchlorhydria	0(0.0%)	2(1.9%)	2(1.0%)
	Nausea	0(0.0%)	1(1.0%)	1(0.5%)
	Vomiting	0(0.0%)	1(1.0%)	1(0.5%)
General disorders and administration site conditions		2(1.9%)	4(3.9%)	6(2.9%)
	Asthenia	0(0.0%)	2(1.9%)	2(1.0%)
	Fatigue	0(0.0%)	1(1.0%)	1(0.5%)
	Oedema peripheral	0(0.0%)	1(1.0%)	1(0.5%)
	Peripheral swelling	1(1.0%)	0(0.0%)	1(0.5%)
	Pyrexia	1(1.0%)	0(0.0%)	1(0.5%)
	Swelling face	1(1.0%)	0(0.0%)	1(0.5%)
Infections and infestations		4(3.9%)	4(3.9%)	8(3.9%)
	Furuncle	0(0.0%)	1(1.0%)	1(0.5%)
	Pharyngitis	1(1.0%)	0(0.0%)	1(0.5%)
	Sinusitis	1(1.0%)	0(0.0%)	1(0.5%)
	Upper respiratory tract infection	0(0.0%)	1(1.0%)	1(0.5%)
	Viral infection	2(1.9%)	2(1.9%)	4(1.9%)
Metabolism and nutrition disorders		1(1.0%)	1(1.0%)	2(1.0%)
	Decreased appetite	0(0.0%)	1(1.0%)	1(0.5%)
	Hypertriglyceridaemia	1(1.0%)	0(0.0%)	1(0.5%)
Musculoskeletal and connective tissue disorders		2(1.9%)	1(1.0%)	3(1.5%)
	Fibromyalgia	1(1.0%)	0(0.0%)	1(0.5%)
	Musculoskeletal pain	0(0.0%)	1(1.0%)	1(0.5%)
	Periarthritis	1(1.0%)	0(0.0%)	1(0.5%)
Nervous system disorders		1(1.0%)	5(4.9%)	6(2.9%)
	Diabetic neuropathy	0(0.0%)	1(1.0%)	1(0.5%)
	Dizziness	0(0.0%)	2(1.9%)	2(1.0%)
	Headache	1(1.0%)	2(1.9%)	3(1.5%)
Respiratory, thoracic and mediastinal disorders		2(1.9%)	0(0.0%)	2(1.0%)
	Cough	1(1.0%)	0(0.0%)	1(0.5%)
	Oropharyngeal pain	1(1.0%)	0(0.0%)	1(0.5%)
Skin and subcutaneous tissue disorders		0(0.0%)	1(1.0%)	1(0.5%)
	Hyperhidrosis	0(0.0%)	1(1.0%)	1(0.5%)

Repaglinide+Voglibose arm:

Of 18 events presented by 15 (14.6%) subjects of RV arm, most were associated with gastrointestinal disorders (5), infections and infestations (4), general disorders and

administration site conditions (3). AEs of other body system SOC were presented by a relatively small study population.

Gastrointestinal Disorders

Diarrhea was reported by 3 (2.9%) subjects, gastritis in 1 (1.0%) subject and abdominal distension in 1 (1.0%) subject.

Infections and infestations

Pharyngitis and sinusitis were reported by 1 (1.0%) subject each, while viral infections were presented by 2 (1.9%) subjects.

General disorders and administration site conditions

Peripheral swelling, pyrexia and swelling face was reported by 1 (1.0%) subject each.

Repaglinide arm

Of 26 events in 19 (18.4%) subjects of R arm, most were associated with gastrointestinal disorders (9), nervous system disorders (5), general disorders and administration site conditions (4), infections and infestations (4). AEs of other body system SOC were presented by a relatively small study population.

Gastrointestinal Disorders

Hyperchlorhydria and gastritis were recorded in 2 (1.9%) subjects each. Abdominal discomfort, abdominal pain upper, diarrhea, nausea and vomiting were recorded in 1 (1.0%) subject each.

Nervous system disorders

Dizziness and headache was reported in 2 (1.9%) subjects each, while diabetic neuropathy was recorded in 1 (1.0%) subject.

General Disorders and Administration Site Conditions

Asthenia was reported in 2 (1.9%) subjects, and fatigue and oedema peripheral in 1 (1.0%) subject each were recorded.

Infections and infestations

Viral infection was reported in 2 (1.9%) subjects and upper respiratory tract infection and furuncle were recorded in 1 (1.0%) subject each.

This study concluded that the safety profile of the FDC of Repaglinide+Voglibose was comparable to Repaglinide monotherapy.

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

As per reported data, Repaglinide had been given with weekly escalating doses from 4-20 mg four times daily in a 6 week period. No safety concerns were raised. As hypoglycaemia in this study was avoided through increased calorie intake, a relative overdose may result in an exaggerated glucose-lowering effect with development of hypoglycaemic symptoms (dizziness, sweating, tremor, headache etc.). Should these symptoms occur, adequate action should be taken to correct the low blood glucose (oral

carbohydrates). More severe hypoglycaemia with seizure, loss of consciousness or coma should be treated with intravenous glucose.

Voglibose competitively and reversibly inhibits the α-glucosidase enzymes (glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestine, which delays the hydrolysis of complex carbohydrates. It is unlikely to produce hypoglycemia in overdose, but abdominal discomfort and diarrhoea may occur.

5 Pharmacological properties

5.3 Mechanism of Action

Repaglinide

Repaglinide is a short-acting oral secretagogue. Repaglinide lowers the blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets.

Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.

Voglibose

Voglibose is an alpha glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border. Inhibition of this enzyme catalyzes the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the post-prandial rise in plasma glucose is blunted in both normal and diabetic subjects resulting in improvement of post prandial hyperglycemia and various disorders caused by hyperglycemia. α-Glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. These agents may be considered as monotherapy in elderly patients or in patients with predominantly post prandial hyperglycemia. α-Glucosidase inhibitors are typically used in combination with other oral antidiabetic agents and/or insulin. Voglibose should be administered at the start of a meal as it is poorly absorbed.

5.4 Pharmacodynamic properties

Repaglinide

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins
ATC code: A10BX02

Voglibose

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins

ATC code: A10BF03

Clinical efficacy

A multicentric, randomized, open-label, comparative, parallel-assignment phase 3 clinical trial was conducted to evaluate the safety and efficacy of fixed dose combinations (FDC) of Repaglinide (0.5mg / 1mg) + Voglibose (0.2mg / 0.3mg) tablets (RV) versus Repaglinide (0.5mg / 1mg) tablets (R) in patients with type 2 diabetes

mellitus. Total 210 patients of Type 2 diabetes mellitus who were inadequately controlled [Glycosylated hemoglobin (HbA1C) ≥ 7.0%] with metformin monotherapy at maximum tolerable stable dose (not less than 1000mg/day) for at least 1 month prior to screening were enrolled in the study. Patients were randomized to one of the two treatment groups in a ratio of 1:1. Total duration of the study was 26 weeks. The study consisted of screening, enrolment and randomization, 24 weeks treatment period followed by 1 week of post treatment follow up.

The least square mean change in PPG from baseline to end of study for ITT population was -54.0194 mg/dL in RV arm and -34.1464 mg/dL in R arm. The difference estimate of this least square mean change between RV and R arms was -19.8729 with the standard error as 8.9468 and 95% CI for difference estimate reported as -37.5426 : -2.2032, Both upper and lower limits of 95% CI lying entirely on improvement side is an evidence of superiority of RV arm. Analysis using two sided test at alpha= 0.05 level of significance exhibited significant effect (p=0.0277) in the RV arm in reducing PPG from baseline to end of treatment as compared to the R arm.

Improvement change from baseline for parameter HbA1C in PP Population in RV arm [68 (85.0%)] was greater than in R arm [63 (72.4%)] while deterioration change was observed more in R arm [24 (27.6%)] w.r.t RV arm [12 (15.0%)]. These reports suggest the superiority of RV arm over R arm. Improvement change in maximum subjects falls under the category reduction >-1 in 74 (44.3%) subjects while in rest of the subjects, the reduction falls between range F> 0 to -1.

The least square mean change in HbA1c from baseline to end of study with Last Observation Carried Forward (LOCF) in the Intention to Treat (ITT) population was -0.8419% in RV arm and -0.3985% in R arm. The difference estimate of this least square mean change between RV and R arms was -0.4434 with the standard error as 0.1725 and 95% CI for difference estimate reported as -0.7837:-0.1031., Both upper and lower limits of 95% CI lying entirely on improvement side is an evidence of superiority of RV arm. Analysis using two sided test at alpha= 0.05 level of significance exhibited significant effect (p=0.0109) in the RV arm in reducing HbA1c from baseline to end of treatment as compared to the R arm.

Iprovement change in HbA1C in ITT (intention to treat) Population in RV (Repaglinide + Voglibose) arm [74(74.7%)] was greater than R (Repaglinide) arm [67(65.0%)] while deterioration change was observed more in R arm [(31(30.1%)] w.r.t RV arm [18(18.2%)]. These reports suggest the superiority of RV arm over R arm. Maximum subjects showed improvement change under category fall > -1 in 79(39.1%) subjects while rest falls between range F > 0 to -1.

The least square mean change in FPG from baseline to end of study for ITT population was -12.2810 mg/dL in RV arm and 0.2286 mg/dL in R arm. The difference estimate of this least square mean change between RV and R arms was -12.5096 with the standard error as 6.1721 and 95% CI for difference estimate reported as -24.6811 : -0.3380. Both upper and lower limits of 95% CI lying entirely on improvement side is an evidence of superiority of RV arm. Analysis using two sided test at alpha= 0.05 level of significance exhibited significant effect (p=0.0440) in the RV arm in reducing FPG from baseline to end of treatment as compared to the R arm.

5.5 Pharmacokinetic properties

Repaglinide

Absorption

Repaglinide is rapidly absorbed from the gastrointestinal tract, which leads to a rapid increase in the plasma concentration of the active substance. The peak plasma level occurs within one hour post administration. After reaching a maximum, the plasma level decreases rapidly.

Repaglinide pharmacokinetics are characterised by a mean absolute bioavailability of 63% (CV 11%).

No clinically relevant differences were seen in the pharmacokinetics of Repaglinide, when Repaglinide was administered 0, 15 or 30 minutes before a meal or in fasting state.

A high inter-individual variability (60%) in Repaglinide plasma concentrations has been detected in the reported clinical trials. Intraindividual variability is low to moderate (35%) and as Repaglinide should be titrated against the clinical response, efficacy is not affected by inter-individual variability.

Distribution

Repaglinide pharmacokinetics are characterised by low volume of distribution, 30 L (consistent with distribution into intracellular fluid) and is highly bound to plasma proteins in humans (greater than 98%).

Elimination

Repaglinide is eliminated rapidly within 4 - 6 hours from the blood. The plasma elimination half-life is approximately one hour.

Repaglinide is almost completely metabolised, and no metabolites with clinically relevant hypoglycaemic effect have been identified.

Repaglinide metabolites are excreted primarily via the bile. A small fraction (less than 8%) of the administered dose appears in the urine, primarily as metabolites. Less than 1% of Repaglinide is recovered in faeces.

Special patient groups

Repaglinide exposure is increased in patients with hepatic insufficiency and in the elderly type 2 diabetic patients. The AUC (SD) after 2 mg single dose exposure (4 mg in patients with hepatic insufficiency) was 31.4 ng/ml x hr (28.3) in healthy volunteers, 304.9 ng/ml x hr (228.0) in patients with hepatic insufficiency, and 117.9 ng/ml x hr (83.8) in the elderly type 2 diabetic patients.

After a 5 day treatment of Repaglinide (2 mg x 3/day) in patients with a severe impaired renal function (creatinine clearance: 20-39 ml/min.), the results showed a significant 2-fold increase of the exposure (AUC) and half-life ($t_{1/2}$) as compared to patients with normal renal function.

Paediatric population

No data are available.

Voglibose

Absorption

Voglibose is poorly absorbed after oral doses. Plasma concentrations after oral doses have usually been undetectable. After an 80 mg dose (substantially higher than recommended dose), peak plasma levels of about 20 ng/mL were observed in 1 to 1.5

hours. When Voglibose tablets were repeatedly administered tohealthy male adults (6 subjects) in a single dose of 0.2 mg, 3times a day, for 7 consecutive days, Voglibose was not detected in plasma or urine. Similarly, when Voglibose was administered to healthy male adults (10 subjects) as a single dose of 2 mg, Voglibose was not detected in plasma or urine.

Distribution
After ingestion of Voglibose (and other glucosidase inhibitors), the majority of active unchanged drug remains in the lumen of the gastrointestinal tract to exert its pharmacological activity.

Metabolism
Voglibose is metabolized by intestinal enzymes and by the microbial flora.

Elimination
Voglibose is excreted in the urine and feces.

In a reported study in which a single dose of 1 mg/kg of C14-Vogliboseswas administered to rats, the transfer of Voglibose to the foetus and to mother's milk was observed, and the rates of excretion into urine and feces were about 5% and 98%,respectively.

6 Nonclinical properties

6.3 Animal Toxicology or Pharmacology

Reported non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Repaglinide was shown not to be teratogenic in reported animal studies. Embryotoxicity, abnormal limb development in rat foetuses and newborn pups, was observed in female rats exposed to high doses in the last stage of pregnancy and during the lactation period. Repaglinide was detected in the milk of animals.

7 Description

Eurepa-V 0.5/0.2
White coloured, uncoated tablets

Eurepa-V 0.5/0.3
Orange coloured, uncoated tablets

Eurepa-V 1/0.2
Yellow coloured, uncoated tablets

Eurepa-V 1/0.3
Pink coloured, uncoated tablets

8 Pharmaceutical particulars

8.3 Incompatibilities

None Stated

8.4 Shelf-life

Do not use later than the date of expiry.

8.5 Packaging information

Available in blister pack of 10 Tablets.

8.6 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture.
Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

9.1 What Eurepa-V is and what it is used for

Eurepa-V is a fixed dose combination of two active ingredients, Repaglinide and Voglibose, the medicines to treat diabetes.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use.

If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Eurepa-V Tablets helps to lower your blood glucose to as normal a level as possible.

Eurepa-V is used for Type 2 Diabetes Mellitus as an adjunct to diet and exercise to improve glycemic control.

9.2 What you need to know before you use Eurepa-V

Do not use Eurepa-V if:

- you are allergic to Repaglinide, Voglibose or to any of the other ingredients of this medicine.
- you have type 1 diabetes.
- the acid level in your blood is raised (diabetic ketoacidosis).
- you have a severe liver disease.
- you take gemfibrozil (a medicine used to lower increased fat levels in the blood).
- you have a gastrointestinal condition in which digested material is prevented from passing normally through the bowel (Gastrointestinal obstruction)
- you have severe infection, before and after operation or with serious trauma

Do not take this medicine if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Eurepa-V.

Warnings and precautions

Talk to your doctor before taking Eurepa-V:

- If you have liver problems. Eurepa-V is not recommended in patients with moderate liver disease. Eurepa-V should not be taken if you have a severe liver disease (see Do not take Repaglinide and Voglibose Tablets).
- If you have kidney problems. Eurepa-V should be taken with caution.
- If you are about to have major surgery or you have recently suffered a severe illness or infection. At such times diabetic control may be lost.
- If you are under 18 or over 75 years of age. Eurepa-V is not recommended. It has not been studied in these age groups.

Talk to your doctor if any of the above applies to you. Eurepa-V may not be suitable for you. Your doctor will advise you.

Children and adolescents
Do not take this medicine if you are under 18 years of age.

If you get a hypo (low blood sugar)
You may get a hypo (short for hypoglycaemia) if your blood sugar gets too low. This may happen:

• If you take too much Eurepa-V

• If you exercise more than usual

• If you take other medicines or suffer from liver or kidney problems

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If your blood sugar is low or you feel a hypo coming on: eat glucose tablets or a high sugar snack or drink, then rest.

When symptoms of hypoglycaemia have disappeared or when blood sugar levels are stabilised continue Eurepa-V treatment.

Tell people you have diabetes and that if you pass out (become unconscious) due to a hypo, they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.

• **If severe hypoglycaemia** is not treated, it can cause brain damage (temporary or permanent) and even death.

• **If you have a hypo** that makes you pass out, or a lot of hypos, talk to your doctor. The amount of Eurepa-V, food or exercise may need to be adjusted.

If your blood sugar gets too high

Your blood sugar may get too high (hyperglycaemia). This may happen:

• If you take too little Eurepa-V

• If you have an infection or a fever

• If you eat more than usual

• If you exercise less than usual.

The warning signs of too high blood sugar appear gradually. They include: increased urination; feeling thirsty; dry skin and dry mouth. Talk to your doctor. The amount of Eurepa-V, food or exercise may need to be adjusted.

Other medicines and Eurepa-V
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Eurepa-V can affect the way some other medicines work. Also some medicines can affect the way Eurepa-V works.

If you take gemfibrozil (used to lower increased fat levels in the blood) you should not take Eurepa-V.

Your body's response to Eurepa-V may change if you take other medicines, especially these:

- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta blockers (used to treat high blood pressure or heart conditions)
- ACE-inhibitors (used to treat heart conditions)
- Salicylates (e.g. aspirin)
- Octreotide (used to treat cancer)
- Nonsteroidal anti-inflammatory drugs (NSAID) (a type of painkillers)
- Steroids (anabolic steroids and corticosteroids – used for anemia or to treat inflammation)
- Oral contraceptives (birth control pills)
- Thiazides (diuretics or 'water pills')
- Danazol (used to treat breast cysts and endometriosis)
- Thyroid products (used to treat low levels of thyroid hormones)
- Sympathomimetics (used to treat asthma)
- Clarithromycin, trimethoprim, rifampicin (antibiotic medicines)
- Itraconazole, ketokonazole (antifungal medicines)
- Gemfibrozil (used to treat high blood fats)
- Ciclosporin (used to suppress the immune system)
- Deferasirox (used to reduce chronic iron overload)
- Clopidogrel (prevents blood clots)
- Phenytoin, carbamazepine, phenobarbital (used to treat epilepsy)
- St. John's wort (herbal medicine)

Eurepa-V with alcohol
Alcohol can change the ability of Eurepa-V to reduce the blood sugar. Watch for signs of a hypo.

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

You should not take Eurepa-V if you are pregnant or you are planning to become pregnant.

You should not take Eurepa-V if you are breast-feeding.

Driving and using machines
Your ability to drive or use a machine may be affected if your blood sugar is low or high. Bear in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car if you:

• Have frequent hypos

• Have few or no warning signs of hypos.

9.3 How to use Eurepa-V

Always take Eurepa-V exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will work out your dose

Ask your pharmacist if you are not sure about the dose to take. The medicine should be taken for the prescribed number of days.

Taking this medicine
• Take this medicine by mouth
• Swallow the tablets with a glass of water immediately before or up to 30 minutes before each main meal.

Do not take more Eurepa-V than your doctor has recommended.

Kidney or liver problems
If you have any kidney or liver problems you may be given a lower dose.

Children and Adolescents:
This medicine should not be given to children or adolescents.

If you take more Eurepa-V than you should
If you take too many tablets, your blood sugar may become too low, leading to a hypo. Please see if you get a hypo on what a hypo is and how to treat it.

If you forget to take Eurepa-V
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Eurepa-V
Be aware that the desired effect is not achieved if you stop taking Eurepa-V. Your diabetes may get worse. If any change of your treatment is necessary contact your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 **Possible Side Effects**

Like all medicines, these suspension can cause side effects, although not everybody gets them.

<u>Hypoglycaemia</u>
The most frequent side effect is hypoglycaemia which may affect up to 1 in 10 patients. Hypoglycaemic reactions are generally mild/moderate but may occasionally develop into hypoglycaemic unconsciousness or coma. If this happens, medical assistance is needed immediately.

Allergy

Allergy is very rare (may affect up to 1 in 10,000 patients). Symptoms such as swelling, difficulty in breathing, rapid heartbeat, feeling dizzy and sweating could be signs of anaphylactic reaction. Contact a doctor immediately.

Other side effects

Common (may affect up to 1 in 10 patients)

• Stomach pain

• Diarrhoea

Rare (may affect up to 1 in 1,000 patients)

• Acute coronary syndrome (but it may not be due to the medicine).

Very rare (may affect up to 1 in 10,000 patients)

• Vomiting

• Constipation

• Visual disturbances

• Severe liver problems, abnormal liver function such as increased liver enzymes in your blood.

Frequency not known

- Hypersensitivity (such as rash, itchy skin, redening of the skin, swelling of the skin)
- Feeling sick (nausea).
- Loose stools,
- Anorexia
- Heartburn
- Abdominal distention
- Increased flatus, and intestinal obstruction like symptoms (a gastrointestinal condition in which digested material is prevented from passing normally through the bowel) due to an increase in intestinal gas.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Eurepa-V

Keep out of the sight and reach of children.

Store at a temperature not exceeding 30°C, protected from light and moisture.

Do not use Eurepa-V after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What Eurepa-V contains:

Eurepa-V 0.5/0.2
The active substance in this product is Repaglinide and Voglibose.

The other ingredients are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone and Magnesium Stearate.

Eurepa-V 0.5/0.3
The active substance in this product is Repaglinide and Voglibose.

The other ingredients are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate, Red oxide of Iron and Yellow oxide of Iron.

Eurepa-V 1/0.2
The active substance in this product is Repaglinide and Voglibose.

The other ingredients are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate and Yellow oxide of Iron.

Eurepa-V 1/0.3
The active substance in this product is Repaglinide and Voglibose.

The other ingredients are Povidone, Meglumine, Poloxamer, Micro crystalline cellulose, Glycerin, Di basic calcium phosphate, Starch, Crospovidone, Magnesium Stearate and Red oxide of Iron.

10 Details of manufacturer
Manufactured by:
Torrent Pharmaceuticals Ltd
32 No. Middle Camp, NH-10,
East District, Gangtok,
Sikkim - 737 135, INDIA

11 Details of permission or licence number with date
M/563/2010 issued on 18.12.2019

12 Date of revision
NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/EUREPA-V 0.5+0.2, 0.5+0.3, 1+0.2, 1+0.3/Nov-2019/01/PI