

# Package Insert

## Glybose 0.3<sup>®</sup>

### Product Summary

#### 1. Name of the medicinal product

Glybose0.3<sup>®</sup>

#### 2. Qualitative and quantitative composition

Each uncoated dispersible tablet contains:

Voglibose IP 0.3 mg

Excipients q.s

#### 3. Pharmaceutical form

Uncoated dispersible tablet

#### 4. Clinical particulars

##### 4.1 Therapeutic indications

For improvement of post prandial hyperglycemia in diabetes mellitus, when only diet and/or exercise or oral hypoglycemic drugs or insulin preparation in addition to diet and/or exercise do not result in adequate glycemetic control.

##### 4.2 Posology and method of administration

###### Normal Adult Dose

Usually, voglibose tablets are orally administered in a single dose of 0.2 mg, 3 times a day, before each meal. If the effect is not sufficient, the quantity of a single dose may be increased up to 0.3 mg.

###### Dosage in Renal Failure

Voglibose is poorly absorbed after oral doses and renal excretion is negligible, suggesting that no dose adjustment is required. However, pharmacokinetic studies in patients with renal insufficiency are not available.

###### Pediatrics

The safety and effectiveness of voglibose in children has not been established.

## Geriatrics

Since elderly patients generally have a physiological hypofunction, it is desirable that such caution be taken as starting the administration at a low dose (eg, 0.1 mg at a time). 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.

### **4.3 Contraindications**

- Hypersensitivity to voglibose, or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Severe infection, before and after operation or with serious trauma.
- Gastrointestinal obstruction or predisposed to it.

### **4.4 Special warnings and precautions for use**

Voglibose tablets dissolve in the mouth and need not be swallowed.

The administration of Voglibose tablets 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). In patients who are being managed with lifestyle modifications (diet and/or exercise), this drug must be given only when the 2-hour post prandial blood glucose levels are  $\geq 200$  mg/dL.

During administration of this drug, disease progression should be closely observed with monitoring of blood glucose levels at regular intervals. If the effect on post prandial glucose levels is not satisfactory even after the administration of this drug for 2 to 3 months (post prandial glucose  $\geq 200$ mg/dL), consider a change to more appropriate treatment.

After administration of this drug, if sufficient control of blood glucose is achieved (post prandial glucose  $\leq 160$  mg/dL) and can satisfactorily be maintained with lifestyle therapy or with additional use of oral hypoglycemic drugs or insulin preparations, the administration of Voglibose tablets should be discontinued, and subsequent progress of disease should be monitored.

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) and 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.
- When patients with diabetes are exposed to unusual stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times insulin therapy may be necessary for some time.

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

When voglibose is used in combination with derivative(s) of sulfonamide, sulfonurea 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.

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: alpha 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 Pregnancy and lactation**

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal 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.

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

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

None reported

#### **4.8 Undesirable effects**

Gastrointestinal adverse effects such as diarrhoea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting, or heartburn may occur with the use of Voglibose.

Also abdominal distention, increased flatus, and intestinal obstruction like symptoms due to an increase in intestinal gas, may occur with use of Voglibose.

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

Elevation of GOT (glutamate oxaloacetate), GPT (glutamatepyruvate transaminase), LDH (lactate dehydrogenase), alpha GPT (alpha glutamate pyruvate) or alkaline phosphatase may infrequently occur.

When Voglibose is used in combination with other antidiabetic drugs, hypoglycemia may occur (0.1% to <5%).

Hypersensitivity: Rash and pruritus may rarely occur. In such a case, Voglibose tablets should be discontinued.

Psychoneurologic: Headache may rarely occur.

Hematologic: Anemia; thrombocytopenia, and leucopenia may rarely occur.

Others: Numbness, edema of face, blurred vision, hot flushes, malaise, weakness,

hyperkalemia, increased serum amylase, decreased HDL cholesterol, diaphoresis or alopecia, and perspiration.

#### **4.9 Overdose**

Voglibose competitively and reversibly inhibits the alpha 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 diarrhea may occur.

### **5. Pharmacological properties**

#### **5.1 Pharmacodynamic properties**

Voglibose is an alpha-glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of alpha-glucosidase in the intestinal brush border. Inhibition of this enzyme halts the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the postprandial 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. Alpha-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. Alpha-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.

Clinical Efficacy:

In a 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 trial, treatment with voglibose in diabetes mellitus patients demonstrated improved post prandial blood glucose levels, a significant decline in 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 meta-analysis comparing miglitol and voglibose, no significant differences in postprandial glucose were observed between the 2 groups.

## **5.2 Pharmacokinetic properties**

### Absorption

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

When voglibose tablets were repeatedly administered to healthy male adults (6 subjects) in a single dose of 0.2 mg, 3 times 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 study in which a single dose of 1 mg/kg of C14-voglibose was administered to rats, the transfer of voglibose to the fetus and to mother's milk was observed, and

the rates of excretion into urine and feces were about 5% and 98%, respectively.

### **5.3 Preclinical safety data**

No animal studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development have been conducted with voglibose.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Sunset Yellow FCF

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Store in a dry & dark place, at a temperature not exceeding 30°C

## **Administrative data**

### **7. Marketing authorisation holder**

Strides Shasun Limited

Strides House, Bilekahalli,

Bannerghatta Road,

Bengaluru – 560 076, India

### **8. Toll free number for reporting**

1800 4190601

### **9. Date of text**

16<sup>th</sup> May 2016