PERMITTED DAILY EXPOSURE FOR VOGLIBOSE

1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Voglibose have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Voglibose is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with diabetes mellitus. Voglibose delays the absorption of glucose thereby reducing the risk of macro vascular complications.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

White to Off White crystalline powder, Voglibose has sweet smell. It is soluble in water and acetic acid, but not easily soluble in methanol, and ethanol, and almost insoluble in ether.

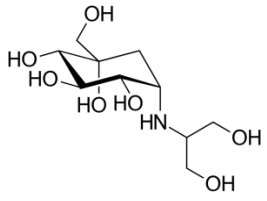
IUPAC name: (1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol

Chemical Abstract Services (CAS) Registry Number: 83480-29-9

Molecular Weight: 267.28 g/mol g·mol−1

Chemical Formula: $C_{10}H_{21}NO_7$

Molecular Structure:



4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	-	√	-

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SUMMARY OF HAZARD IDENTIFICATION:

Pharmacodynamics data

Voglibose is an α-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 halts the decomposition of disaccharides into monosaccharide's 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 postprandial 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 mono therapy in elderly patients or in patients with predominantly postprandial hyperglycemia.
α-glucosidase inhibitors are typically used in combination with other oral anti diabetic agents and/or insulin. Voglibose should be administered at the start of a meal as it is poorly absorbed.

Pharmacokinetics data

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 1-1.5 hrs. 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.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Rat	LD_{50}	Oral	20000	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 25(815), 1994
Rat	LD_{50}	Intravenous	6300	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 25(815), 1994
Mouse	LD_{50}	Oral	14700	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 25(815), 1994
Mouse	LD_{50}	Intravenous	7820	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 25(815), 1994
Dog	LD_{50}	Oral	2000	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 25(815), 1994

Repeated Dose Toxicity (Chronic Toxicity)

No data available.

Carcinogenicity

No data available.

In vivo/In vitro Genotoxicity Studies

No data available.

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:	
Reproductive/Developmental Toxicity	No data available.
Highly Sensitizing Potential	Sensitivity to skin is very rare.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	**Clinical Therapeutic Dose:** Usual Adult Dose: Voglibose dispersible Tablets are orally administered in a single dose of 0.2 mg three times daily just before each meal. If the effect is not sufficient enough, the single dose may be increased up to 0.3 mg. **Adverse Effects:** Blurred Vision Feeling of Sickness Feeling of Discomfort Increased Intestinal Gas Numbness Abdominal Pain

NOAEL/LOAEL	0.004 mg/kg/day (Minimum therapeutic dose) considered as NOAEL value.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	5	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	Repeated Dose toxicity data not available.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.004 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 0.00008 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Voglibose
- https://www.ndrugs.com/?s=voglibose&t=actions
- http://www.torrentian.com/pisheet/Upload/PI_Sheet/1229.pdf
- https://www.ncbi.nlm.nih.gov/pubmed/9918384