PERMITTED DAILY EXPOSURE FOR GLIMEPIRIDE

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 Glimepiride 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:

Glimepiride is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder formulated into tablets of 1-mg, 2-mg, and 4-mg strengths for oral administration.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

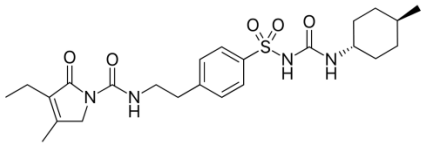
IUPAC name: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1 carboxamido) ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.

Chemical Abstract Services (CAS) Registry Number: 93479-97-1

Molecular Weight: 490.62

Chemical Formula: $C_{24}H_{34}N_4O_5S$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

PURE & CURE HEALTHCARE PVT. LTD., HARIDWAR	**DETERMINATION OF PERMISSIBLE DAILY EXPOSURE (PDE) FOR GLIMEPIRIDE (ORAL DOSAGE)**

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	A mild glucose-lowering effect first appeared following single oral doses as low as 0.5 - 0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [Tmin]) was about 2 to 3 hours. In type 2 diabetes (formerly known as non-insulin-dependent diabetes mellitus or NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours. In larger dose-ranging studies, blood glucose and glycosylated hemoglobin (HbA1C) were found to respond in a dose-dependent manner over the range of 1 to 4 mg of AMARYL once daily. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of AMARYL up to 8 mg once daily. No difference in the decrease in blood glucose and HbA1C concentrations were found when AMARYL was administered once or twice daily. In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA1C for AMARYL patients treated with 8 mg once daily was 2.0% (0.02) in absolute units compared with placebo-treated patients. Efficacy results were not affected by age, gender, weight, or race. In a 22-week, randomized, placebo-controlled study of Type 2 diabetic patients unresponsive to dietary management, AMARYL therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA1C. The results of three long-term studies demonstrated that AMARYL, when administered over a prolonged treatment period of one-year (n = 986), was effective in maintaining metabolic control in type 2 diabetic patients who were responders to sulfonylurea therapy. In an extension of long-term trials with patients previously treated with AMARYL, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA1C levels was seen after up to 2.5 years of AMARYL therapy (n = 445). Combination therapy with AMARYL and metformin was compared with AMARYL and metformin monotherapy in Type 2 diabetic patients. The results of the study indicated that the combination of metformin and AMARYL was more effective than either treatment alone, with regards to improving HbA1C, fasting blood glucose and postprandial blood glucose levels. Combination therapy with AMARYL and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was > 130% of their ideal body weight. Initially, 5-10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the AMARYL/insulin therapy group showed an insulin sparing effect with a use of 38% less insulin. AMARYLtherapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for Type 2 diabetes.
Pharmacokinetics data	**Absorption:** After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean Tmax (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, respectively). In normal healthy volunteers, the intraindividual variabilities of Cmax, AUC, and total body clearance after oral dosing (Cl/F) for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively. The pharmacokinetics of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, doseproportionality (4 and 8 mg) study in patients with type 2 diabetes are summarized **below:**

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SUMMARY OF HAZARD IDENTIFICATION:	
	These data indicate that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in type 2 diabetic patients. Oral clearance of glimepiride did not change over the 1-8-mg dose range, indicating linear pharmacokinetics. **Distribution:** After intravenous dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%. **Metabolism:** Glimepiride is completely metabolized by oxidative biotransformation after either IV or oral administration. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful in humans is not clear. Genetic polymorphisms may reduce the metabolic capability of 2C9. Some clinical studies in a limited number of subjects have shown that genetic polymorphisms of CYP2C9 affect the pharmacokinetics of AMARYL and that the carriers of CYP2C9*3 variant (3-8.5% of Caucasians) may have lower (18-75%) oral clearance and 1.3 to 5.2-fold higher exposure (AUC(0-∞)) of AMARYL. Individuals expressing this variant genotype may therefore be predisposed to have an increased response to AMARYL. Moreover, the CYP2C9 *3/*3 and *2/*3 genotypes may have an increased risk of hypoglycemia. **Excretion:** When 14C-glimepiride was given as a single dose orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and metabolites M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and metabolites M1 and M2 (predominant) accounted for about 70% of that Page 21 of 49 recovered in feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Species	Route	Dose (mg/kg)	No. Deaths/No. per Group (M,F)	Observations
Mouse	PO	10,000	0/5, 0/5	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	PO	10,000	0/5, 0/5	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	IP	4,000	0/3, 0/3	A dose of 4,000 mg/kg was tolerated without deaths. Reduced motility and retracted flanks were observed.
Mouse	IP	2,000	1/5, 0/5 0/5, 0/5 0/5, 0/5	Acute Lethal Dose >2,000 mg/kg IP for glimepiride, M1, and M2.
	PO	2,000 500 1,000 2,000 2,000	0/5, -/- 0/5, -/- 0/5, -/- 6/7, -/- 0/5, -/-	Acute Lethal Doses: glimepiride: >2,000 mg/kg HOE 490D (decomposition product): 1,000 - 2,000 mg/kg HOE 490I (impurity): >2,000 mg/kg
Rat	PO	10,000	0/5, 0/5	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	PO	5,000	0/2, 0/2	Transient, increased salivation was seen in the females only.
	PO	5,000	0/2, 0/2	Transient, increased salivation was seen in the females only.
	PO	2,000	0/5, 0/5	Sunken flanks, squatting posture, stilted gait, and irregular respiration were observed in both sexes.
	IP	3,950	0/3, 0/3	A dose of 3,950 mg/kg was tolerated without deaths. Reduced motility, squatting position and retracted flanks were observed.
Dog	PO	2,000	0/2, -/-	Acute Lethal Dose >2,000 mg/kg

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Species	No. of animals per group (M,F)	Route	Dose levels	Duration	Key Observations
Rat	15, 15	PO	0, 1.0, 50, 2500 mg/kg/day	4 weeks	Clinical, hematological and clinico-chemical investigations revealed no pathological changes. Histological examination revealed that none of the doses of glimepiride administered led to any morphological changes.
	10, 10	PO	0, 1000, 2500 mg/kg/day	1 month	The **"No Observed Effect Level" was at 1,000 mg/kg body weight per day**. However, there were no signs of clear toxicity detectable at the dose of 2,500 mg/kg body weight per day.
	5, 5	PO	0, 40, 200, 1000 mg/kg/day	28 days	No compound-related macroscopically visible changes were observed at necropsy. Histopathological examination revealed focal cell necroses of the liver in three females of the high dose group. The "no observed effect level" was 40 mg/kg body weight per day
	50, 50	PO	0, 20, 1000, 50,000 ppm	12 months	Body weight development of male rats was slightly impaired at 1000 ppm and 50,000 ppm and in the females at 50000 ppm, but feed consumption was not affected. Clinical examinations, hematological and clinico-chemical analysis, urinalysis and macroscopic inspection did not yield any compound related pathological findings. In females, heart weights were significantly decreased (all doses), liver weights decreased (1,000 ppm) and spleen weights increased (50,000 ppm). Histological examination did not reveal any compound-related morphological organ changes among treatment groups.
	20,20	Feed	0, 1.0, 50, 2500 mg/kg/day	6 months	The clinical, hematological and clinico-chemical investigation revealed no pathological changes due to study drug. The death of three animals in the 2500 mg/kg group was deemed independent of the compound. Histological examination revealed marked degranulation of the beta cells after 50 or 2,500 mg/kg. This finding was reversible within the four-week recovery period.
	5, 5	IV	0, 0.1, 1.0, 10.0 mg/kg	14 days	All doses tested were tolerated symptom-free. The clinical, haematological, clinico-chemistry or histological examinations revealed no further compound-induced changes.
	5, 5	IV	0, 0.1, 1.0, 10.0 mg/kg	14 days	The clinical examinations gave no indication of compound-induced changes. The macroscopic and microscopic examination did not reveal compound-induced organ changes.
	15, 15	IV	0, 0.1, 1.0, 10.0 mg/kg day	4 weeks	The 0.1 and 1.0 mg/kg doses were tolerated without the occurrence of any pathological changes. After 10 mg/kg there were no clinical, hematological, or clinico-chemistry changes. Histological examination revealed dose-dependent degranulation of the beta cells in the Islets of Langerhans at all doses. This finding was still present at the end of the four-week recovery period and is connected to the pharmacodynamics effect of the compound.
Dog	3, 3	PO	0, 0.8, 16.0, 320 mg/kg/day	4 weeks	There were no relevant toxicological impairments in any of the dosage groups. A female from the highest dosage group showed a slight alteration in feed uptake.
	5, 5	PO	0, 0.8, 16.0, 320 mg/kg/day	26 weeks	The administration of HOE-490 in doses of 0.8 mg/kg and 16.0 mg/kg in dogs did not lead to any relevant toxicological changes. In the highest dosage group, only a slight loss in body weight for two animals was observed. In addition, on histological examination, a degranulation of the beta cells was revealed in all dosage groups (reversible within recovery period).
	6, 6	PO	0, 0.8, 16.0, 320 mg/kg/day	12 months	In the highest dosage group, bilateral posterior subcapsular cataracts were observed in one male and one female at the end of the study. Very marked aggravation of the lens opacity was observed in the female whose recovery was prolonged to 12 weeks after the study. Microscopic examination revealed no histological correlate to the ophthalmological changes observed in the male and unilateral ocular degeneration of a few lens fibres in the female. In addition, on histological examination, a degranulation of the beta cells was revealed in all dosage groups.
	3, 3	IV	0, 0.08, 0.4, 2.0 mg/kg	2 weeks	No compound-induced toxic changes were detected in any of the dosage groups. The only pharmacological effect observed was a slight dose-dependent reduction in serum glucose at 0.40 and 2.0 mg/kg M1.
	3, 3	IV	0, 0.08,	4 weeks	No compound-related toxicological effects in any of the study groups were observed. As the

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SUMMARY OF HAZARD IDENTIFICATION:

Carcinogenicity

Species/Strains	No. animals/ Group (M, F)	Dosage/Delivery Route	Duration	Observations
Mouse	48, 48	320, 1,265 ppm in feed	2 weeks (toxicokinetics)	validated exposure to drug in carcinogenicity study
	10, 10	0, 200, 1,000, 5,000, 25,000, 50,000 ppm in feed	3 months (dose-finding)	5,000 ppm chosen as top dose for carcinogenicity study due to saturated absorption
	50, 50	0, 320, 1,265, 5,000 ppm in feed	24 months (carcinogenicity)	no demonstrated carcinogenicity
Rat	3, 3	0, 320, 1,000, 5,000, 10,000, 50,000 ppm in feed	3 months (dose-finding)	320 ppm chosen as top dose for carcinogenicity study (008166) as it caused maximum degranulation of β cells
	10, 10	0, 320, 1,000, 5,000, 10,000, 25,000, 50,000 ppm in feed	3 months (dose-finding)	5,000 ppm chosen as top dose for carcinogenicity study (009620) due to saturated absorption
	50, 50	0, 32, 100, 320 ppm in feed	30 months (carcinogenicity)	no demonstrated carcinogenicity
	50, 50	0, 320, 1,265, 5,000 ppm in feed	30 months (carcinogenicity)	no demonstrated carcinogenicity

In vivo/In vitro Genotoxicity Studies

Study Type	Dose	Observation
In vitro Non-mammalian Ames	4-10,000 µg/plate	Negative
	4-5,000 µg/plate	Negative
	4-5,000 µg/plate (glimepiride-sulfonamide)	Negative
	4-5,000 µg/plate (glimepiride-*cis*-isomer)	Negative
	4-5,000 µg/plate (glimepiride-urethane)	Negative
	4-5,000 µg/plate (glimepiride-ethylurethane)	Negative
In vitro Mammalian HGPRT in V79 Chinese Hamster Cells	50-600 µg/mL	Negative
In vitro Mammalian Unscheduled DNA Synthesis	1-1,000 µg/mL	Negative
In vitro Mammalian Chromosome Aberrations in V79 Chinese Hamster Cells	10-1,250 µg/mL (glimepiride-urethane)	Negative
	10-1,060 µg/mL (glimepiride-ethylurethane)	Negative
	10-100 µg/mL (glimepiride-sulfonamide)	Negative
In vivo Mammalian Chromosome Analysis of Chinese Hamster	0-5,000 mg/kg PO	Negative
In vivo Mammalian Mouse - Micronucleus	400 mg/kg PO	Negative
	2,500 mg/kg PO	Negative

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SUMMARY OF HAZARD IDENTIFICATION:

	(glimepiride-sulfonamide)	
	2,000 mg/kg PO (glimepiride-*cis*-isomer)	Negative

Reproductive/Developmental Toxicity

Species/Strain	Route	Dosage	No. of animal group	Observations
Fertility Studies				
Mouse	PO	0, 250, 2,500 mg/kg	7 M	No effects on male fertility
Rat	Feed	0, 20, 1,000, 50,000 ppm	32 F	No effects on fertility. Postnatal effects on humerus in 1 adult offspring at 1,000 ppm and in 11 adult offspring from 7 litters at 50,000 ppm.
Teratology Study				
Rat	PO	0, 1, 50, 2,500 mg/kg	35 F	No effect on pregnancy, parturition or intrauterine development of foetuses, other than uni- or bilateral microphthalmia seen in 2 and 4 fetuses in 1 and 50 mg/kg groups, which was due to pharmacolo-gically induced hypoglycemia.
Rabbit	PO	0.0067, 0.0212, 0.0670, 0.32, 3.2, 32 mg/kg From the 6th-18th day of pregnancy	15 F	Hypoglycemia during pregnancy and in fetuses with doses of 0.0067 and 0.0212 mg/kg. Higher doses induced persistent hypoglycemia, intolerance, modified feed consumption and body weight, abortion, no of uterine death. Some surviving fetuses experienced eye malformation, sternal and abdominal fissures, and/or bends of the ulna, tibia, and fibula, and shortening or bends of the femur. All findings were attributed to hypoglycemia.
Rabbit	PO	0, 0.32 mg/kg/day HOE 490 or 0.96 mg/kg/day glibenclamide	15 F	Both compounds produced marked, persistent hypoglycemia. Normal pregnancies were observed in 14/15 in the control group, 5/15 in HOE 490 group, and 2/15 in glibenclamide group
	PO	0, 0.32 mg/kg/day HOE 490 or 0.96 mg/kg/day glibenclamide	15 F	Abortion/foetal loss in 5/15 dams treated with HOE 490, 9/15 with glibenclamide, and 1/15 controls. Hypoglycemia was considered to be cause of foetal deaths.
Rabbit	PO	0, 3, 15 mg/kg/day HOE 490 or 50 mg/kg/day (b.i.d.) gliclazide	4-12 F	Both drugs produced hypoglycemia and increased incidences of abortions.
Rabbit: Himalayan and New Zealand White	PO	0.32 mg/kg/day	15 F 19 F	Himalayan rabbits showed more hypoglycemia*)* and higher abortion rate (11/15) than New Zealand White rabbits (2/19)

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SUMMARY OF HAZARD IDENTIFICATION:

	Perinatal and Postnatal Studies				
	Rat Hoe:WISKf (SPF71)	PO	0, 1, 50, 2,500 mg/kg	20-22 F	Dose-dependent increase in intrauterine foetal death in 50 and 2,500 mg/kg groups. Shortening and bending of right humerus of 1 pup from 2,500 mg/kg group.
		Feed	0, 50,000 ppm	15 F	Pups exposed to HOE 490 in breast milk attained serum levels about twice that of the mothers. Dosage regimen increased number of stillbirths and retarded body weight development of pups.
		Feed	0, 20, 1,000, 5,000 ppm	10-30 F	Effects on humerus and femorus detected by day 4 post-partum. Intrauterine exposure affected bones only slightly
		PO	0, 2,500 mg/kg	10 F	Exposure during lactation produced severe bone deformities.
		Feed	50,000 ppm	40 F	Slight increase in retarded fetuses in offspring delivered by caesarean section. The rearing group exhibited a slight increase in the number of death births and reduced body weight development in second and third week of lactation.
Highly Sensitizing Potential	In clinical trials, allergic reactions such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of Glimepiride-treated patients. There are post marketing reports of more serious allergic reactions (e.g. dyspnea, hypotension, shock).				

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IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Hypoglycemia during pregnancy.
Clinical therapeutic and adverse effects	**Starting Dose:** The usual starting dose of Glimepiride as initial therapy is 1 mg once daily, administered with breakfast or the first main meal. **Maintenance Dose:** The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 1 mg at 1-2 week intervals based upon the patient's blood glucose response. **Adverse effect:** low blood sugar (hypoglycemia), Symptoms may include: trembling or shaking, nervousness or anxiety, irritability, sweating, lightheadedness or dizziness, headache, fast heart rate or palpitations, intense hunger, fatigue or tiredness.

NOAEL/LOAEL	1000 mg/kg/day shall be 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	1 months duration study in rodent (Shirt duration).
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 (Maximum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{1000 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 20 mg/day

5. REFERENCES:

- http://products.sanofi.ca/en/amaryl.pdf
- https://en.wikipedia.org/wiki/Glimepiride
- https://www.sandoz.ca/sites/www.sandoz.ca/files/Sandoz%20Glimepiride%20PMe%2020170301.pdf