PERMITTED DAILY EXPOSURE FOR IVABRADINE

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 Ivabradine 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:

Ivabradine is a medication used for the symptomatic management of stable heart-related chest pain and heart failure not fully managed by beta blockers. Ivabradine acts by reducing the heart rate via specific inhibition of the pacemaker current, a mechanism different from that of beta blockers and calcium channel blockers, two commonly prescribed antianginal drugs. Ivabradine is a cardiotonic agent.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Ivabradine hydrochloride is a white to slightly yellow powder. It is freely soluble in water.

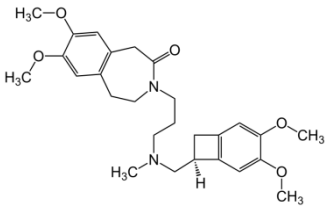
IUPAC name: 3-[3-[[(7*S*)-3, 4-dimethoxy-7-bicyclo [4.2.0]octa-1,3,5-trienyl]methyl-methylamino]propyl]-7,8-dimethoxy- 2,5-dihydro-1*H*-3-benzazepin-4-one

Chemical Abstract Services (CAS) Registry Number: 155974-00-8

Molecular Weight: 468.6 g/mol

Chemical Formula: $C_{27}H_{36}N_2O_5$

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	Ivabradine causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses >20 mg twice daily. In a study of subjects with preexisting conduction system disease (first- or second-degree AV block or left or right bundle branch block) requiring electrophysiologic study, IV Ivabradine (0.20 mg/kg) administration slowed the overall heart rate by approximately 15 bpm, increased the PR interval (29 msec), and increased the AH interval (27 msec). Ivabradine does not have negative inotropic effects. Ivabradine increases the uncorrected QT interval with heart rate slowing but does not cause rate-corrected prolongation of QT
Pharmacokinetics data	▪ **Absorption:** Following oral administration, peak plasma ivabradine concentrations are reached in approximately 1 hour under fasting conditions. The absolute oral bioavailability of ivabradine is approximately 40% because of first-pass elimination in the gut and liver. Food delays absorption by approximately 1 hour and increases plasma exposure by 20% to 40%. Ivabradine should be taken with meals. ▪ **Distribution:** Ivabradine is approximately 70% plasma protein bound, and the volume of distribution at steady state is approximately 100 L. ▪ **Metabolism:** The pharmacokinetics of ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours. ▪ **Elimination:** The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.
Acute Toxicity	**Acute and chronic toxicity:** The oral administration of Ivabradine in rats was associated with lesions affecting the eyes (retinal degeneration). Retinal degeneration was observed after 8-weeks treatment at doses of 10 mg/kg/day (0.5 times the MRHD based on BSA comparison). Juvenile rats were more sensitive to the Ivabradine-induced effects, especially on eyes and kidneys, than adult rats with retinal degeneration occurring at doses ≥ 2.15 mg/kg/day (0.1 times the MRHD based on BSA comparison), and reversible damage to proximal tubule epithelium occurring at doses ≥ 4.64 mg/kg/day (0.2 times the MRHD based on BSA comparison).
Repeated Dose Toxicity (Chronic Toxicity)	**Study 1:** In repeat dose toxicity studies, histological evidence of anestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to Ivabradine for 1 month or more at

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SUMMARY OF HAZARD IDENTIFICATION:	
	exposures 0.3-times the AUC observed in patients at the recommended dose of 80 mg. Findings in the ovaries seen following 1 month of dosing exhibited evidence of reversibility. In a female fertility study in rats, administration of Ivabradine from 2 weeks prior to mating through Day 8 of gestation at a dose of 20 mg/kg/day (approximately 1.5-times the human Cmax at the recommended dose of 80 mg/day) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility when females were mated 1 month after treatment discontinuation. **Study 2:** **In dogs given Ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year**, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated Ih currents in the retina, which share extensive homology with the cardiac pacemaker If current. Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.
Carcinogenicity	There was no evidence of carcinogenicity when mice and rats received Ivabradine up to 104 weeks by dietary administration. High doses in these studies were associated with mean Ivabradine exposures of at least 37 times higher than the human exposure (AUC0-24hr) at the MRHD.
In vivo/In vitro Genotoxicity Studies	Ivabradine tested negative in the following assays: bacterial reverse mutation (Ames) assay, in vivo bone marrow micronucleus assay in both mouse and rat, in vivo chromosomal aberration assay in rats, and in vivo unscheduled DNA synthesis assay in rats. Results of the in vitro chromosomal aberration assay were equivocal at concentrations approximately 1,500 times the human Cmax at the MRHD. Ivabradine tested positive in the mouse lymphoma assays and in vitro unscheduled DNA synthesis assay in rat hepatocytes at concentrations greater than 1,500 times the human Cmax at the MRHD.
Reproductive/Developmental Toxicity	In pregnant rats, oral administration of ivabradine during the period of organogenesis (gestation day 6-15) at doses of 2.3, 4.6, 9.3, or 19 mg/kg/day resulted in fetal toxicity and teratogenic effects. Increased intrauterine and post-natal mortality and cardiac malformations were observed at doses ≥ 2.3 mg/kg/day (equivalent to the human exposure at the MRHD based on AUC0-24hr). Teratogenic effects including interventricular septal defect and complex anomalies of major arteries were observed at doses ≥ 4.6 mg/kg/day (approximately 3 times the human exposure at the MRHD based on AUC0-24hr).
Highly Sensitizing Potential	No any sensitivity observed.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	The oral administration of Ivabradine in rats was associated with lesions affecting the eyes (retinal degeneration).
Clinical therapeutic and adverse effects	**<u>Usual Adult Dose for Congestive Heart Failure</u>** **Initial dose:** 5 mg orally twice a day with meals **Maximum dose:** 7.5 mg orally twice a day Overall, 14.5% of patients taking Ivabradine experience luminous phenomena (by patients described as sensations of enhanced brightness in a fully maintained visual field). This is probably due to blockage of Ih ion

	channels in the retina, which are very similar to cardiac If. These symptoms are mild, transient, and fully reversible. In clinical studies, about 1% of all patients had to discontinue the drug because of these sensations, which occurred on average 40 days after the drug was started. In a large clinical trial, bradycardia (unusually slow heart rate) occurred in 2% and 5% of patients taking ivabradine at doses of 7.5 and 10 mg respectively (compared to 4.3% in those taking atenolol). 2.6–4.8% reported headaches. Other common adverse drug reactions (1–10% of patients) include first-degree AV block, ventricular extra systoles, dizziness and/or blurred vision.

NOAEL/LOAEL	Exposures in male and female rats at the No Observed Adverse Effect Level (NOAEL) of 7.5 mg/kg/day

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 year duration study in rodent.
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.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	
CALCULATION		
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{7.5 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 0.15 mg/day	

5. REFERENCES:

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209964lbl.
- https://www.ebmconsult.com/articles/monograph-Ivabradine
- https://pubchem.ncbi.nlm.nih.gov/compound/Ivabradine#section=Computed-Descriptors
- https://www.cdc.gov/niosh/review/peer/isi/pdfs/Reviewers-Comments-and-NIOSH-response-hazdrug2018.
- https://en.wikipedia.org/wiki/Ivabradine.
- https://www.drugs.com/dosage/ivabradine.html