PERMITTED DAILY EXPOSURE FOR ESCITALOPRAM OXALATE

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 Escitalopram Oxalate 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:

Escitalopram Oxalate is the oxalate salt of escitalopram, a pure S-enantiomer of the racemic bicyclic phthalane derivative citalopram, with antidepressant activity. As a selective serotonin reuptake inhibitor (SSRI), escitalopram blocks the reuptake of serotonin by neurons in the central nervous system (CNS), thereby potentiating CNS serotonergic activity.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

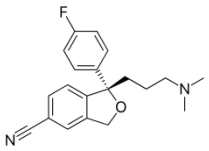
IUPAC name: (S)-1-[3-(Dimethylamino) propyl]-1-(4-fluorophenyl)-1, 3-dihydroisobenzofuran-5-carbonitrile

Chemical Abstract Services (CAS) Registry Number: 128192-01-0

Molecular Weight: 324.392 g/mol

Chemical Formula: $C_{20}H_{21}FN_2O$

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	In vitro and in vivo studies in animals suggest that Escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with Escitalopram. Escitalopram has no or very low affinity for serotonergic (5-HT1-7) or other receptors including alpha- and beta-adrenergic, dopamine (D1-5), histamine (H1-3), muscarinic (M1-5), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na+, K+, Cl- , and Ca++ channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.
Pharmacokinetics data	The single- and multiple-dose pharmacokinetics of Escitalopram is linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of Escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent. Absorption and Distribution Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food. The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable. The binding of escitalopram to human plasma proteins is approximately 56%.
Acute Toxicity	After gavage administration, Escitalopram 500 mg/kg caused deaths, prostration and tremors, 250 mg/kg had no effect. Citalopram also had no effect at 250 mg/kg, but 500 and 1000 mg/kg were both associated with some deaths and similar clinical signs. Bolus IV injection of escitalopram at 22 mg/kg led to breathing difficulties within 30 minutes and 30 mg/kg caused convulsions and deaths. Citalopram had similar effects at those dose levels.
Repeated Dose Toxicity (Chronic Toxicity)	Comparative 4 and 13-week and bridging oral tests have been conducted with Escitalopram and racemic citalopram in the rat. A separate 60-day test was also carried out using the rat as a model. In the 4-week experiment, the highest dose of both drugs (60 mg/kg/day) led to small retardation in weight gain, slight changes in liver function and phospholipidosis in various tissues. At a dose of 60 mg/kg/day, the signs of phospholipidosis were more marked in animals given racemic citalopram. In the 13-week toxicity experiments in the rat, it was demonstrated that the pattern of toxic actions of escitalopram was similar to that of citalopram. Toxic actions mainly comprised hepatic enlargement and inflammation of the myocardium at high dose levels, plus typical phospholipidosis seen with many cationic amphophilic medicines. There were also clinical signs including reduced weight gain, sedation and trembling. The NOEL was about 5-10 mg/kg/day for both compounds.

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SUMMARY OF HAZARD IDENTIFICATION:	
Carcinogenicity	**Study 1:** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. **The relevance of these findings to humans is unknown.** **Study 2:** Comprehensive carcinogenicity tests of racemic citalopram were done in the mouse and rat. Racemic citalopram showed no evidence of carcinogenic potential in the NMRI/BOM strain of mice at daily doses of 40-240 mg/kg (1.5 years) and in the COBS WI strain of rats at 8-80 mg/kg (2 years) other than an increased incidence of small intestine carcinoma in rats treated with 8 and 24 mg/kg/day of racemic citalopram. The latter doses are approximately equivalent to a dose of escitalopram 2-6 times the maximum recommended human daily dose based on mg/m2 basis. No such effects were observed in rats treated with a 80 mg/kg/day dose. On the same grounds as used previously, it can be concluded that escitalopram is not carcinogenic.
In vivo/In vitro Genotoxicity Studies	**Study 1:** Racemic citalopram was mutagenic in the in vitro bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the in vitro Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the in vitro mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled in vitro/in vivo unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the in vitro chromosomal aberration assay in human lymphocytes or in two in vivo mouse micronucleus assays. **Study 2:** An extensive battery of in vitro and in vivo tests of racemic citalopram has been conducted. Racemic citalopram did not show mutagenic activity in most of the in vitro tests (Ames Salmonella assay; chromosome aberration assay in cultured human lymphocytes; gene mutation assay in cultured mouse lymphoma L5178Y) and in vivo tests (micronucleus test; unscheduled DNA synthesis). However, racemic citalopram was mutagenic in the in vitro bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. Racemic citalopram was clastogenic in the in vitro Chinese hamster lung cell assay, in the presence and absence of metabolic activation.
Reproductive/Developmental Toxicity	**Study 1:** When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **Study 2:** When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 16, 32, 48 and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at dose ≥32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. Tests of the maternal and foetal toxicity and the peri- and

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SUMMARY OF HAZARD IDENTIFICATION:	
	post-natal toxicity of escitalopram were performed in rats. One high dose of racemic citalopram was included for comparison. In an embryo-fetal developmental toxicity study with escitalopram (56, 112, or 150 mg/kg/day) and racemic citalopram (70 mg/kg/day) in female rats during the period of organogenesis embryo-foetal effects (reduced foetal body weight and delays in ossification) were found only at doses ≥ 112 mg/kg/day (approximately ≥ 56 times the maximum recommended human dose of 20 mg/day escitalopram on a body surface area [mg/m2] basis). Similar effects were seen with racemic citalopram. These doses were also associated with maternal toxicity. In a previous separate embryo-foetal developmental toxicity study with racemic citalopram embryo-fetal effects in terms of decreased foetal growth and survival, an increased incidence of foetal abnormalities (including cardiovascular and skeletal defects, and delays in ossification) were noted at 112 mg/kg/day (approximately 18 times the maximum recommended human dose of 60 mg/day citalopram on a body surface area [mg/m2] basis). In an embryo-fetal developmental toxicity study with racemic citalopram (0.8, 3.2 or 12.8 mg/kg/day in female rabbits during the period of organogenesis no effects on embryo-foetal development were noted. The NOEL for maternal toxicity was 3.2 mg/kg/day and 12.8 mg/kg/day for developmental toxicity. When female rats were orally treated with escitalopram (6, 12, 24, or 48 mg/kg/day) or racemic citalopram (12 or 48 mg/kg/day) during pregnancy and through weaning, the high doses were associated with increased offspring mortality in the first 4 days and persistent offspring growth retardation at 48 mg/kg/day for both compounds. The NOEL for maternal and reproductive toxicity of citalopram was 12 mg/kg/day. The corresponding NOEL and NOAEL for escitalopram for reproductive and maternal effects were 24 mg/kg/day, which is approximately 12 times the maximum recommended human dose on mg/m^2 basis.
Highly Sensitizing Potential	Escitalopram Oxalate is not sensitive to skin.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Does not show any indication of adverse effect seen in non-clinical studies.
Clinical therapeutic and adverse effects	**Initial:** 10 mg once daily **Recommended:** 10 mg once daily **Maximum:** 20 mg once daily

NOAEL/LOAEL	NOAEL value considered 5 mg

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)	5	Duration study in rodent (13 weeks or 3 months).
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	

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CALCULATION	
PDE Calculation	NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg) F1 x F2 x F3 x F4 x F5 = 5 (NOAEL) x 50 5 x 10 x 5 x 1 x 5 = 0.2 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Escitalopram.
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.
- https://pubchem.ncbi.nlm.nih.gov/compound/Escitalopram-oxalate
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