PERMITTED DAILY EXPOSURE FOR ARIPIPRAZOLE

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 **Aripiprazole** 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:

Aripiprazole is an atypical antipsychotic. It is primarily used in the treatment of schizophrenia and bipolar disorder. Other uses include as an add-on treatment in major depressive disorder, tic disorders and irritability associated with autism. It is taken by mouth or injection into a muscle. Common side effects include vomiting, constipation, sleepiness, dizziness, weight gain and movement disorders. Serious side effects may include neuroleptic malignant syndrome, tardive dyskinesia and anaphylaxis. It is not recommended for older people with dementia-related psychosis due to an increased risk of death. In pregnancy, there is evidence of possible harm to the baby. It is not recommended in women who are breast feeding

3. IDENTITY OF THE ACTIVE SUBSTANCE:

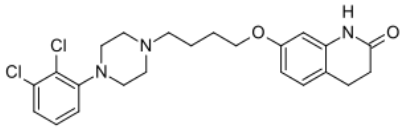
IUPAC NAME: 7-{4-[4-(2, 3-Dichlorophenyl) piperazin-1-yl] butoxy}-3, 4-dihydroquinolin-2(1H)-one.

Chemical Abstract Services (CAS) Registry Number: 129722-12-9

Molecular Weight: 448.385 g/mol g·mol−1

Chemical Formula: $C_{23}H_{27}C_{l2}N_3O_2$

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	Aripiprazole's mechanism of action is different from those of the other FDA-approved atypical antipsychotics (e.g., clozapine, olanzapine, Quetiapine, ziprasidone, and Risperidone). It shows differential engagement at the dopamine receptor (D_2). It appears to show predominantly antagonist activity on postsynaptic D_2 receptors and partial agonist activity on presynaptic D_2 receptors, D_3, and partially D_4) and is a partial activator of serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_6, and 5-HT_7). It also shows lower and likely insignificant effect on histamine (H_1), epinephrine/norepinephrine (α), and otherwise dopamine (D_4), as well as the serotonin transporter. Aripiprazole acts by modulating neurotransmission overactivity of dopamine, which is thought to mitigate schizophrenia symptoms. It appears to show predominantly antagonist activity on postsynaptic D_2 receptors and partial agonist activity on presynaptic D_2 receptors. Aripiprazole is also a partial agonist of the D_3 receptor. In healthy human volunteers, D_2 and D_3 receptor occupancy levels are high, with average levels ranging between approximately 71% at 2 mg/day to approximately 96% at 40 mg/day. Most atypical antipsychotics bind preferentially to extrastriatal receptors, but Aripiprazole appears to be less preferential in this regard, as binding rates are high throughout the brain.[61] Aripiprazole is also a partial agonist of the serotonin 5-HT_{1A} receptor (intrinsic activity = 68%). It is a very weak partial agonist of the 5-HT_{2A} receptor (intrinsic activity = 12.7%), and like other atypical antipsychotics, displays a functional antagonist profile at this receptor. The drug differs from other atypical antipsychotics in having higher affinity for the D_2 receptor than for the 5-HT_{2A} receptor. At the 5-HT_{2B} receptor, Aripiprazole acts as a potent inverse agonist. Unlike other antipsychotics, Aripiprazole is a high-efficacy partial agonist of the 5-HT_{2C} receptor (intrinsic activity = 82%) and with relatively weak affinity; this property may underlie the minimal weight gain seen in the course of therapy. At the 5-HT_7 receptor, Aripiprazole is a very weak partial agonist with barely measurable intrinsic activity, and hence is a functional antagonist of this receptor. Aripiprazole also shows lower but likely clinically insignificant affinity for a number of other sites, such as the histamine H_1, α-adrenergic, and dopamine D_4 receptors as well as the serotonin transporter, while it has negligible affinity for the muscarinic acetylcholine receptors. Since the actions of Aripiprazole differ markedly across receptor systems Aripiprazole was sometimes an antagonist (e.g. at 5-HT6 and D2L), sometimes an inverse agonist (e.g. 5-HT2B), sometimes a partial agonist (e.g. D2L), and sometimes a full agonist (D3, D4). Aripiprazole was frequently found to be a partial agonist, with an intrinsic activity that could be low (D2L, 5-HT2A, 5-HT7), intermediate (5-HT1A), or

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SUMMARY OF HAZARD IDENTIFICATION:	
	high (D4, 5-HT2C). This mixture of agonist actions at D2-dopamine receptors is consistent with the hypothesis that Aripiprazole has 'functionally selective' actions. The 'functional-selectivity' hypothesis proposes that a mixture of agonist/partial agonist/antagonist actions are likely. According to this hypothesis, agonists may induce structural changes in receptor conformations that are differentially 'sensed' by the local complement of G proteins to induce a variety of functional actions depending upon the precise cellular milieu. The diverse actions of Aripiprazole at D2-dopamine receptors are clearly cell-type specific (e.g. agonism, antagonism, partial agonism), and are most parsimoniously explained by the 'functional selectivity' hypothesis. Since 5-HT2C receptors have been implicated in the control of depression, OCD, and appetite, agonism at the 5-HT2C receptor might be associated with therapeutic potential in obsessive compulsive disorder, obesity, and depression. 5-HT2C agonism has been demonstrated to induce anorexia via enhancement of serotonergic neurotransmission via activation of 5-HT2C receptors; it is conceivable that the 5-HT2C agonist actions of Aripiprazole may, thus, be partly responsible for the minimal weight gain associated with this compound in clinical trials. In terms of potential action as an antiobsessional agent, it is worthwhile noting that a variety of 5-HT2A/5-HT2C agonists have shown promise as antiobsessional agents, yet many of these compounds are hallucinogenic, presumably due to 5-HT2A activation. Aripiprazole has a favorable pharmacological profile in being a 5-HT2A antagonist and a 5-HT2C partial agonist. Based on this profile, one can predict that Aripiprazole may have antiobsessional and anorectic actions in humans. Wood and Reavill's (2007) review of published and unpublished data proposed that, at therapeutically relevant doses, Aripiprazole may act essentially as a selective partial agonist of the D_2 receptor without significantly affecting the majority of serotonin receptors. A positron emission tomography imaging study found that 10 to 30 mg/day Aripiprazole resulted in 85 to 95% occupancy of the D_2 receptor in various brain areas (putamen, caudate, ventral striatum) versus 54 to 60% occupancy of the 5-HT_{2A} receptor and only 16% occupancy of the 5-HT_{1A} receptor. It has been suggested that the low occupancy of the 5-HT_{1A} receptor by Aripiprazole may have been an erroneous measurement however. Aripiprazole acts by modulating neurotransmission overactivity on the dopaminergic mesolimbic pathway, which is thought to be a cause of positive schizophrenia symptoms. Due to its agonist activity on D_2 receptors, Aripiprazole may also increase dopaminergic activity to optimal levels in the mesocortical pathways where it is reduced.
Pharmacokinetic data	**Absorption:** Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet

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SUMMARY OF HAZARD IDENTIFICATION:	
	formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of Aripiprazole. **Distribution:** Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, Aripiprazole and dehydro-Aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin. **Biotransformation:** Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma. **Elimination:** The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6. The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic. Following a single oral dose of [14C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.
Acute Toxicity	
Repeated Dose Toxicity (Chronic Toxicity)	• Dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose. • An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of Aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in

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SUMMARY OF HAZARD IDENTIFICATION:	
	human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of *in vitro* solubility. • In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development. • Based on results of a full range of standard Genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity. • Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.
Carcinogenicity	Lifetime carcinogenicity studies were conducted in ICR mice, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m2 , respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m2). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m2). Proliferative changes in the pituitary and mammary gland of rodents

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	have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.
In vivo/In vitro Genotoxicity Studies	The mutagenic potential of aripiprazole was tested in the in vitro bacterial reverse-mutation assay, the in vitro bacterial DNA repair assay, the in vitro forward gene mutation assay in mouse lymphoma cells, the in vitro chromosomal aberration assay in Chinese hamster lung (CHL) cells, the in vivo micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the in vitro chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the in vitro assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the in vivo micronucleus assay in mice; however, the response was due to a mechanism not considered relevant to humans.
Reproductive/Developmental Toxicity	Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day. Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.
Highly Sensitizing Potential	

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	
Clinical therapeutic and adverse effects	

NOAEL/LOAEL	

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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	Short 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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{200 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 4 mg/day

5. CONCLUSION: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, Genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. REFERENCES:

- https://en.wikipedia.org/wiki/Aripiprazole/
- https://www.medicines.org.uk/emc/product/3546/smpc#gref/
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf