PERMITTED DAILY EXPOSURE FOR ALFUZOSIN

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 **Alfuzosin** 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:

Alfuzosin, is a medication of the α1 blocker class. It is used to treat benign prostatic hyperplasia (BPH). As an antagonist of the α1 adrenergic receptor, it works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

White to off-white crystalline powder. Alfuzosin is readily soluble in water.

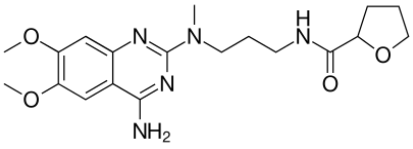
IUPAC NAME: (RS)-N-[3-[(4-Amino-6, 7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl] tetrahydrofuran-2-Carboxamide.

Chemical Abstract Services (CAS) Registry Number: 81403-80-7

Molecular Weight: 389.456 g·mol−1

Chemical Formula: $C_{19}H_{27}N_5O_4$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Alfuzosin is a quinazoline-derivative alpha-adrenergic blocking agent used to treat hypertension and benign prostatic hyperplasia. Accordingly, Alfuzosin is a selective inhibitor of the alpha subtype of alpha adrenergic receptors. In the human prostate, Alfuzosin antagonizes phenylephrine (alpha agonist)-induced contractions, *in vitro*, and binds with high affinity to the alpha adrenoceptor,

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SUMMARY OF HAZARD IDENTIFICATION:

which is thought to be the predominant functional type in the prostate. Studies in normal human subjects have shown that Alfuzosin competitively antagonized the pressor effects of phenylephrine (an alpha) agonist) and the systolic pressor effect of norepinephrine. The antihypertensive effect of Alfuzosin results from a decrease in systemic vascular resistance and the parent compound Alfuzosin is primarily responsible for the antihypertensive activity.

Pharmacokinetic data

Mechanism of action: Alfuzosin is a non-subtype specific alpha-adrenergic blocking agent that exhibits selectivity for alpha-adrenergic receptors in the lower urinary tract. Inhibition of these adrenoreceptors leads to the relaxation of smooth muscle in the bladder neck and prostate, resulting in the improvement in urine flow and a reduction in symptoms in benign prostate hyperplasia. Alfuzosin also inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation.

Absorption: Absorption is 50% lower under fasting conditions.

Volume of Distribution: 3.2 L/kg (healthy male middle-aged volunteers).

Metabolism: Hepatic. Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylations, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Route of Elimination: Following oral administration of 14C-labeled Alfuzosin solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in feces and 24% in urine.

Acute Toxicity

The results of single dose toxicity studies in Mice and Rats after oral and intra-peritoneal administration are summarized in the table below:

Species	Route	Sex	LD_{50} (mg/kg)
Mouse	Oral	M & F (10, 20, 40, 60 mice/sex)	2300 + 94 in males 1950 ± 79 in females
Rat		M & F (10, 20 rats/sex)	≥ 4000 in males 3000 in females
Mouse	Intraperitoneal	M & F (20 mice/sex)	600 ± 25 in males 650 ± 20 in females
Rat		M & F (10, 20 rats/sex)	480 in males and females

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

The chronic toxicity of orally administered Alfuzosin was studied in rats and dogs in 1 month and 3 month toxicity studies. In addition, chronic oral toxicity was evaluated in rats up to 6 months. The dosages administered in these studies are given in the table below:

Study	Alfuzosin doses in mg/kg/day (Oral administration)
1 week intravenous study in rats (5M, 5F/dose group)	30, 60 and 100
1 week intravenous study in dogs (1M, 1F/dose group)	10, 15 and 30 mg/kg bid
1 month intravenous study in rats (3M, 3F/dose group)	2, 10 and 50
1 month oral study in rats (12M, 12F/ dose group)	30, 100 and 400 in males 100, 200 and 400 in females
1 month intravenous study in dogs (3M, 3F/dose group)	2, 5 and 20 mg/kg bid
1 month oral study in dogs (1M, 1F/ dose group)	5, 100 and 200 as gelatin capsules 60 for 1 week then 100 for 3 weeks
1 month study in dogs (2M, 2F/dose group)	50, 100 and 200 as gelatin capsules
1 month study in dogs (3M, 3F/dose group)	20 mg/animal of 5 mg SR tablets
3 month toxicity in rats (20M, 20F/ dose group)	5, 30 and 200
3 month study in dogs (3M, 3F/dose group)	5, 20 and 80
6 month toxicity in rats (25M, 25F/ dose group)	10, 50 and 250
1 year study in rats (20M, 20F/dose group)	1, 5 and 25
1 year study in dogs (7M, 7F/dose group)	5, 20 and 80

In the 1 week intravenous studies in rats, 3 animals died on days 1, 3 and 5 as a result of severe cardiac depression. Survivors exhibited prostration, dyspnea, sialorrhea, peripheral vasodilation and palpebral ptosis. No lesions were observed at injection sites. When dogs were administered Alfuzosin intravenously for one week, no deaths occurred and clinical symptoms consisted of peripheral vasodilation, nasal dryness, diarrhea, hypotonia, tremor, protrusion of the nictitating membrane and hyperdacryorrhea. Palpebral ptosis was observed at 15 and 30 mg/kg bid with vomiting and salivation occurring at 30 mg/kg bid. In a one month intravenous study in dogs, no deaths occurred and no lesions were evident at injection sites. However clinical symptoms such as peripheral vasodilation, palpebral ptosis, nasal dryness, tachypnea, tachycardia and some hypotonia, vomiting, and ptyalism were recorded.
In one month oral studies in rats, clinical signs began to appear at 100 mg/kg/

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SUMMARY OF HAZARD IDENTIFICATION:	
	day for males and 200 mg/kg/day for females and consisted mainly of sedation, hypersalivation, slight changes in haematology as well as increased triglycerides. When rats were treated by i.v. route with 2, 10 or 50 mg/kg/day Alfuzosin three deaths occurred in the first week. Clinical symptoms included palpebral ptosis, hypotonia, ocular secretions, peripheral vasodilation, respiratory difficulties and vaginal dilation. Beagle dogs treated with 200 mg/kg/day for 4 weeks demonstrated motor incoordination and loss of appetite accompanied by a reduction in water intake. A dose of 200 mg/kg/day also produced an increase in SGPT, proteinuria, haematuria and renal lesions. When dogs were treated with 60 mg/kg/day for one week followed by 100 mg/kg/day for 3 weeks, clinical symptoms were mild and consisted of vomiting and diarrhea, tremor, sedation, vasodilation, palpebral ptosis and abnormal gait. Similar symptoms were observed in dogs treated for 3 months with 80 mg/kg/day. When dogs were treated with the 5 mg SR formulation for one month (20 mg/animal/day) no clinical signs and no deaths were observed. Body weight and food consumption were normal. In addition, dogs treated with 2, 5 or 20 mg/kg bid by IV route demonstrated typical clinical symptoms but no deaths were observed. In 3 month toxicity studies in rats, 200 mg/kg /day caused transient hypersalivation, mild anaemia, increased urine output and weight changes of adrenal glands and spleen in males. When dogs were treated with Alfuzosin 5, 20 or 80 mg/kg/day for 3 months, no deaths occurred and clinical symptoms included soft feces, vomiting, tremor, peripheral vasodilation and hyper salivation at 20 and 80 mg/kg/day. In addition, abnormal quietness was observed at all doses. Rats treated with Alfuzosin for 6 months demonstrated marked accumulation of the compound in blood and histopathological changes in adrenal tissue at 50 mg/kg/day in males and 250 mg/kg/day in females as well as liver cell changes such as necrosis of cells around acinus and cytoplasmic eosinophilia. In this 6 month toxicity study, rats of both sexes were divided into four groups and administered 10, 50 or 250 mg/kg/day Alfuzosin or control. Twenty-two animals died out of which 4 cases were considered not related to treatment. The deaths were dose-related (2 males at 50 mg/kg/day, 7 males and 9 females at 250 mg/kg/day). Rats administered 250 mg/kg/day and 2 males at 50 mg/kg/day died within 30 minutes after oral gavage and exhibited respiratory difficulties, hypersalivation and peripheral vasodilation prior to death. The other animals died between 2 and 22 hours following administration of Alfuzosin. Alfuzosin also caused ptosis and peripheral vasodilation from Week 1 and peripheral redness of the eyes and vaginal dilation from Week 2. Rats receiving 50 and 250 mg/kg/day showed a dose-related frequency of salivation (from Week 2) and urogenital wetness (from Week 7). Food consumption slightly increased in all animals with the exception of males receiving 250 mg/kg/day who lost all appetite from Week 9. When rats were treated with Alfuzosin 1, 5 or 20 mg/kg/day for one year clinical symptoms were ptosis at 5 and 25 mg/kg/day and scrotal reddening and vaginal dilation in all treatment groups. Increased weight gain was observed in females at 25 mg/kg/day after Month 1. Food consumption was increased in males at the two higher doses and females at 25 mg/kg/day. Water consumption

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SUMMARY OF HAZARD IDENTIFICATION:	
	was normal. Twelve animals died or were sacrificed, however 8 cases were not treatment related. Organ weight examination revealed increases in the pituitary gland in females, the kidney and thyroid in males and the liver and spleen in both sexes. Oral administration of Alfuzosin to dogs for 53 weeks is characterized by a fairly wide range of clinical symptoms such as photophobia, tremor, palbebral ptosis, nasal dryness and soft feces. However laboratory and physiological tests did not show any treatment related effects. Macroscopic and microscopic examinations revealed impairment of the female reproductive cycle.
Carcinogenicity	There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100 mg/kg/day Alfuzosin for 98 weeks in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose. Likewise, there was no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100 mg/kg/day Alfuzosin for 104 weeks in females and males, respectively. Carcinogenicity studies were carried out in the mouse and rat. Alfuzosin was shown to have no carcinogenic effect. In a 98-week oral carcinogenicity study in mice, Alfuzosin was administered at doses with vehicle control to groups of 51 males and 51 females in 2 sub-groups. Mortality was increased in males at 100 mg/kg/day (53% in controls, 78% in the 100 mg/kg/day group). There were very slight increases in the relative weight of the liver in a few males who received 100 mg/kg/day of Alfuzosin. No tumoral or other types of lesions were observed. At doses up to 100 mg/kg/day, Alfuzosin had no carcinogenic potential in mice. In a 104-weeks oral carcinogenicity study in rats, Alfuzosin was administered at doses of 10, 30 and 100 mg/kg/day, with vehicle control, to groups of 50 males and 50 females in 2 sub-groups. Mortality was comparable in all doses. **No oncogenic effect was noted.**
In vivo/In vitro Genotoxicity Studies	Alfuzosin showed no evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and in vivo mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line. Alfuzosin was administered in vitro to cultures of hepatocytes from males Sprague Dawley rats and male Beagle dogs at concentration from 1.25 to 100 µM. Findings were similar in both species: Alfuzosin induced gradual membrane and metabolic damage. However the IC50 was >100 µM. Alfuzosin was otherwise well tolerated by hepatocytes at these concentrations.
Reproductive/Developmental Toxicity	There was no evidence of reproductive organ toxicity when male rats were given Alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days. Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively although this did not result in impaired fertility in rats. **Teratogenicity:** There was no evidence of teratogenicity or embryotoxicity in rats at maternal (oral gavage) doses up to 250 mg/kg/day. In rabbits, up to the

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SUMMARY OF HAZARD IDENTIFICATION:	
	dose of 100 mg/kg/day given orally (via gavage), **no evidence of fetal toxicity or teratogenicity was seen.** Gestation was slightly prolonged in rats with a maternal dose >5 mg/kg/day (oral gavage) but there were no difficulties with parturition. Studies were carried out in the Sprague Dawley rat and the New Zealand rabbit. Alfuzosin was not embryotoxic, produced no teratogenic effects and did not affect fertility, parturition or lactation at dose levels many-fold greater than therapeutic levels in man. A preliminary fertility study in **Sprague Dawley rats** established that the maximum dose to be used in the principal fertility study should be < 200 mg/kg/day. The principal study utilized groups of 26 male and female animals who received Alfuzosin by gavage at doses of 5, 25 and 125 mg/kg/day, with vehicle control. Males were treated from Day 71 prior to mating to the end of gestation of the female. Females were treated from Day 15 prior to mating to Day 21 postcoitum and half of the females to Day 25 post-partum. The vaginal cytological cycle was altered at doses of 25 and 125 mg/kg/day of Alfuzosin, but **Alfuzosin had not effect on mating, ovulation or pre- and post-natal development. The "No Adverse Effect Level" for the F0 generation was 5 mg/kg/day.** The viability of the offspring was reduced at a dose of 125 mg/kg/day but the reproductive behaviour of the F1 generation was not changed following treatment of the parents. Consequently, the "No Adverse Effect Level" for the F1 and F2 generations was considered to be 25 mg/kg/day. In a peri- and post-natal study in the rat, Alfuzosin was administered from Day 15 post-coitum to Day 21 post-partum at doses of 5, 25 and 125 mg/kg/day, with vehicle control, to groups of 20 females. Alfuzosin at these doses caused no abnormalities in parents or pups. The **"No Adverse Effect Level" for the F0 generation was 5 mg/kg/day** and for the F1 generation was 125 mg/kg/day. Teratogenicity studies were carried out in the rat and rabbit. **Alfuzosin produced no teratogenic effects.** Alfuzosin was administered by gavage to three groups of females rats at various dose levels, with vehicle control, from Day 6 to Day 15 of gestation. In a preliminary study, 15 animals received 100 or 200 mg/kg/day. In the main study, 20 animals received 10, 50 or 250 mg/kg/day. These studies showed no effect of Alfuzosin on organogenesis up to a dose of 250 mg/kg/day. The "No Adverse Effect Level" for the F0 and F1 generations was 250 mg/kg/day. Alfuzosin was administered by gavage to two groups of females rabbits at various dose levels, with vehicle control from Day 6 to Day 18 of gestation. In a preliminary study, 4 animals received 50, 100 or 250 mg/kg/day. In the main study, 14 animals received 10, 30 or 100 mg/kg/day. These studies showed no effect of Alfuzosin on organogenesis up to a dose of 100 mg/kg/day. The "No Adverse Effect Level (NOAEL)" for the F0 generation was 10 mg/kg/day and for the F1 generation was 30 mg/kg/day.
Highly Sensitizing Potential	**Rare side effects:** A Skin Disorder With Blistering And Peeling Skin Called Toxic Epidermal Necrolysis.

IDENTIFICATION OF CRITICAL EFFECTS:

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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:** For oral dosage form (extended release tablets): • For benign prostatic hyperplasia (BPH): o Adults -10 milligrams (mg) once a day. o Children - Use is not recommended. **Adverse effect:** The most common side effects are dizziness (due to postural hypotension), upper respiratory tract infection, headache, fatigue, and abdominal disturbances. Side effects include stomach pain, heartburn, and congested nose. Adverse effects of Alfuzosin are similar to that of Tamsulosin with the exception of retrograde ejaculation.

NOAEL/LOAEL	Alfuzosin had not effect on mating, ovulation or pre- and post-natal development. The "No Adverse Effect Level" for the F0 generation was 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	Short duration study in rodent (pre & post natal development).
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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{5 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 0.1 mg/day

5. REFERENCES:

- https://pubchem.ncbi.nlm.nih.gov/compound/2092.
- https://www.drugbank.ca/drugs/DB00346.
- http://products.sanofi.ca/en/xatral.pdf
- https://www.mayoclinic.org/drugs-supplements/alfuzosin-oral-route/side-effects/drg-20061611?p=1.
- https://www.webmd.com/drugs/2/drug-77236/alfuzosin-oral/details/list-sideeffects.