PERMITTED DAILY EXPOSURE FOR MONTELUKAST SODIUM

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 Montelukast Sodium 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:

Montelukast is a medication used in the maintenance treatment of asthma. It is generally less preferred for this use than inhaled corticosteroids. It is not useful for acute asthma attacks. Other uses include allergic rhinitis and hives of long duration. For allergic rhinitis it is a second line treatment. It is taken by mouth.

Common side effects include abdominal pain, cough and headache. Severe side effects may include allergic reactions, such as anaphylaxis and eosinophilia. Use in pregnancy appears to be safe. Montelukast is in the leukotriene receptor antagonist family of medications. It works by blocking the action of leukotriene D4 in the lungs resulting in decreased inflammation and relaxation of smooth muscle.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

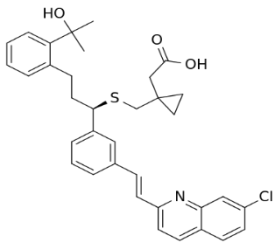
IUPAC name: (R,E)-2-(1-((1-(3-(2-(7-Chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl) propylthio)methyl)cyclopropyl)acetic acid

Chemical Abstract Services (CAS) Registry Number: 158966-92-8

Molecular Weight: 586.184 g/mol g·mol−1

Chemical Formula: $C_{35}H_{36}ClNO_3S$

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	Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), Montelukast sodium inhibited early-and late-phase bronchoconstriction due to antigen challenge by 75% and 57% respectively. Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β-agonist. Clinical studies in adults 15 years of age and older demonstrated there is no additional clinical benefit to Montelukast doses above 10 mg once daily. This was shown in two chronic asthma studies using doses up to 200 mg once daily and in one exercise challenge study using doses up to 50 mg, evaluated at the end of the once daily dosing interval. The effect of montelukast sodium on eosinophils in the peripheral blood was examined in clinical trials in adults and pediatric (6 to 14 years of age) asthmatic patients. Montelukast sodium decreased mean peripheral blood eosinophils approximately 13% to 15% from baseline compared with placebo over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received Montelukast sodium, a median decrease of 13% in peripheral blood eosinophil counts was noted, compared with placebo, over the double-blind treatment periods. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. Although the pharmacokinetics of Montelukast are similar whether dosed in the morning or the evening, efficacy was demonstrated in clinical trials in adults and pediatric patients in which Montelukast was administered in the evening without regard to the time of food ingestion.
Pharmacokinetics data	**Absorption:** Montelukast is rapidly absorbed following oral administration. For the 10 mg film coated tablet, the mean peak plasma concentration (Cmax) is achieved in 3 to 4 hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are neither influenced by a standard meal in the morning nor by a high fat snack in the evening. Safety and efficacy were demonstrated in clinical trials where the 4 mg chewable tablet, the 5 mg chewable tablet, and the 10 mg film-coated tablet were administered in the evening without regard to the timing of food ingestion. The safety of Montelukast Sodium was also demonstrated in a clinical study in which the 4 mg oral granules were administered in the evening without regard to the timing of food ingestion. For the 5 mg chewable tablet, the Cmax is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning. However, food does not have a clinically important influence with chronic administration of the

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SUMMARY OF HAZARD IDENTIFICATION:	
	chewable tablet. The comparative pharmacokinetics of Montelukast when administered as two 5 mg chewable tablets versus one 10 mg film-coated tablet has not been evaluated. For the 4 mg chewable tablet, Cmax is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state. The 4 mg oral granule formulation was shown to be bioequivalent to the 4 mg chewable tablet when administered to healthy adults in the fasted state. Bioequivalence was also demonstrated when the granules were administered with applesauce. The co-administration of a high fat meal decreased the rate of absorption (Cmax 112.8 versus 175.4 ng/mL with and without a high fat meal, respectively), although the extent of absorption was not affected by food (AUCT 1133.8 versus 1119.2 ng·hr/mL with and without a high fat meal, respectively). **Distribution:** Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of Montelukast averages 8 to 11 liters . Studies in rats with radiolabeled Montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues. Metabolism: Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of Montelukast are undetectable at steady state in adults and pediatric patients. In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8 and 2C9 are involved in the metabolism of Montelukast. CYP2C8 appears to play a major role in the metabolism of Montelukast at clinically relevant concentrations. **Excretion:** The plasma clearance of Montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled Montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of Montelukast oral bioavailability, this indicates Montelukast and its metabolites are excreted almost exclusively via the bile. In several studies, the mean plasma half-life of Montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of Montelukast are nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10 mg Montelukast, there is little accumulation of the parent drug in plasma (~14%).
Acute Toxicity	Cases of acute over dosage with Montelukast have been reported in both adults and children with doses as high as 1000 mg. However, clinical and biological signs in such cases were relatively benign and included a headache, thirst, somnolence or hyperactivity, vomiting, and abdominal pain.
Repeated Dose Toxicity (Chronic Toxicity)	The toxic potential of Montelukast Sodium was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in monkeys and rats and up to 14 weeks in infant monkeys and in mice. Montelukast Sodium was

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SUMMARY OF HAZARD IDENTIFICATION:	
	well tolerated at doses which provide a wide margin of safety based on total dose administered. **The no effect level was evaluated to be 150 mg/kg/day in female monkeys, 300 mg/kg/day in male monkeys, 50 mg/kg/day in rats, >150 mg/kg/day in infant monkeys and 50 mg/kg/day in mice.** For all toxicological parameters, the no effect level was at least 125 times the recommended human dose (determined using mg/kg/day values). There were no findings that would preclude administration at the therapeutic dosage level for both adults and pediatric patients.
Carcinogenicity	**No evidence of tumorigenicity** was seen in a 2-year carcinogenicity study in Sprague-Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (approximately 160 times the maximum recommended daily oral doses in adults and 190 times the maximum recommended daily oral dose in children, on a mg/m^2 basis) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (approximately 40 times the maximum recommended daily oral dose in adults and 50 times the maximum recommended daily oral dose in children, on a mg/m^2 basis).
In vivo/In vitro Genotoxicity Studies	**Montelukast demonstrated no evidence of mutagenic** or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the in vitro mouse bone marrow chromosomal aberration assay.
Reproductive/Developmental Toxicity	In fertility studies in female rats, Montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (approximately 160 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis) and in rabbits at oral doses up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral doses in adults, on a mg/m^2 basis). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Montelukast should be used during pregnancy only if clearly needed.
Highly Sensitizing Potential	**Montelukast** is one of the commonly used drugs in asthma patients. It is prescribed along with inhalational corticosteroids. Although a relatively safe drug, there is a probability of occurrence of **skin** rashes and skin bruising.

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IDENTIFICATION OF CRITICAL EFFECTS:	
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	**Dosage:** 10 mg once a day. **Adverse effects:** Neuropsychiatric events have been reported in patients receiving Montelukast. These events have been noted in adults, teenagers, and younger patients, and include among others: anxiety, depression, aggressiveness, agitation, attention and memory impairment, sleeping disorders (insomnia, somnambulism, dream anomalies), seizures, paresthesia, hypoesthesia, as well as suicidal thoughts and behavior. During treatment with Montelukast, some patients with asthma may develop systemic eosinophilia, sometimes associated with vasculitis, consistent with Churg-Strauss syndrome (rare). This event may be associated with the decrease of oral corticosteroid doses. However, the fact that Montelukast is the causative agent of these systemic manifestation has not been established. Other adverse effects of Montelukast include (among others): • Headaches, fever, fatigue • Upper respiratory signs (rhinorrhea, pharyngitis, laryngitis, sinusitis, epistaxis) • Auricular signs: otitis • Lower respiratory signs: a cough, pneumonia, wheezing • Ocular signs: conjunctivitis • Gastrointestinal signs (nausea, diarrhea, vomiting, abdominal pain, dyspepsia, pancreatitis) • Hepato-biliary signs: liver injury (hepatocellular and mixed-pattern), cholestatic hepatitis • Infections (influenza, varicella) • Dermatologic manifestations (pruritus, eczema and atopic dermatitis, angioedema, urticaria, skin rash, bruising, erythema multiforme, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome) • Musculoskeletal signs: Arthralgia, myalgia • Hypersensitivity manifestations: anaphylaxis, eosinophilic infiltration of the liver • Biologic anomalies: thrombocytopenia, increased plasmatic alanine aminotransferase

NOAEL/LOAEL	The no effect level was evaluated to be 50 mg/kg/day in rats for 52 weeks studies.

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)	1	52 weeks 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	The no effect level was evaluated to be 50 mg/kg/day in rats for 52 weeks studies.
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 = 50 (NOAEL) x 50 5 x 10 x 1 x 1 x 5 = 10 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Montelukast
- https://www.sandoz.ca/sites/www.sandoz.ca/files/MONTELUKAST_PM_English20160105.pdf
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