PERMITTED DAILY EXPOSURE FOR LEVOCETIRIZINE HCL

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 Levocetirizine Hydrochloride 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:

Levocetirizine is an antihistamine used for the treatment of allergic rhinitis (hay fever) and long term hives of unclear cause. It is less sedating than older antihistamines. It is taken by mouth. Common side effects include sleepiness, dry mouth, cough, vomiting, and diarrhea. Use in pregnancy appears safe but has not been well studied and use when breastfeeding is of unclear safety. It is classified as a second-generation antihistamine and works by blocking histamine H1-receptors.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Levocetirizine dihydrochloride, USP is a white, or almost white powder and is freely soluble in water, practically insoluble in acetone and methylene chloride.

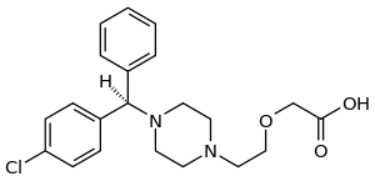
IUPAC name: 2-(2-{4-[(R)-(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid

Chemical Abstract Services (CAS) Registry Number: 130018-77-8

Molecular Weight: 388.88 g/mol g·mol−1

Chemical Formula: $C_{21}H_{25}ClN_2O_3$

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	Levocetirizine is a third generation, non-sedating, selective histamine H1 receptor antagonist, with antihistamine, anti-inflammatory and potential anti-angiogenic activities. Levocetirizine competes with endogenous histamine for binding at peripheral H1-receptor sites on the effector cell surface. This prevents the negative symptoms associated with histamine release and an allergic reaction. In addition, as histamine plays an important role in angiogenesis during an allergic inflammatory reaction, blocking the action of histamine may modulate the expression of proangiogenic factors and thus may prevent angiogenesis. As a third-generation histamine H1 receptor antagonist, Levocetirizine has fewer side effects than most second-generation antihistamines.
Pharmacokinetics data	Levocetirizine exhibited linear pharmacokinetics over the therapeutic dose range in adult healthy subjects. **Absorption:** Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on the extent of exposure (AUC) of the Levocetirizine tablet, but T_{max} was delayed by about 1.25 hours and C_{max} was decreased by about 36% after administration with a high fat meal; therefore, Levocetirizine can be administered with or without food. A dose of 5 mg (10 mL) of Levocetirizine dihydrochloride oral solution is bioequivalent to a 5 mg dose of Levocetirizine dihydrochloride tablets. Following oral administration of a 5 mg dose of Levocetirizine dihydrochloride oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hour post dose. **Distribution:** The mean plasma protein binding of Levocetirizine in vitro ranged from 91 to 92%, independent of concentration in the range of 90 ng/mL to 5,000 ng/mL, which includes the therapeutic plasma levels observed. Following oral dosing, the average apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water. **Metabolism:** The extent of metabolism of Levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily medicated by CYP3A4 while aromatic oxidation

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SUMMARY OF HAZARD IDENTIFICATION:	
	involves multiple and/or unidentified CYP isoforms. **Elimination:** The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for Levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of Levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of Levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of Levocetirizine is reduced.
Acute Toxicity	The acute maximal non-lethal oral dose of Levocetirizine was 240 mg/kg in mice (approximately 190 times the maximum recommended daily oral dose in adults, approximately 230 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 180 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m_2 basis). In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults, approximately 460 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 370 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). Acute toxicities were conducted in mice rats and dogs. In mice and rats, the toxicity was determined by the oral and intravenous routes. By the oral route, the doses in mice were 240, 560, 1300 and 3200 mg/kg. All doses showed toxic signs beginning with quiet behavior, jerky breathing, ptosis, arched back and piloerection at 240 mg/kg. As the doses increased the toxicity increased leading to death at 560 (3/10) mg/kg and at 1300 (8/10). At 3200 mg/kg, the animals manifested cyanosis prior to death. By the intravenous route, the doses were 130, 190, 270 and 390 mg/kg. At all doses there was tail necrosis at the site of injection except at 390 mg/kg in which death was fairly quickly. At 190 mg/kg, there were signs of toxicity manifested by quiet behavior, jerks, tachynpea breathing, ventral lying position and unsteady gait, but no mortality. At 270 mg/kg, 8/10 and at 390 mg/kg all mice (10/10) died within 1-2 minutes. In another study, the acute intravenous toxicity of levocetirizine, S-cetirizine and cetirizine were compared. The toxicity profile of the three compounds was similar. However, the incidence of mortality was similar to levocetirizine and cetirizine and both of their incidences at lower doses were lower than S-cetirizine. In rats, the oral doses were 100, 240 560 and 1300 mg/kg. Signs of toxicity were seen at 240 mg/kg as manifested by bradynpea, jerky breathing, ptosis, piloerection, ventral lying position, muscle weakness, dyspnea, muscle hypertonicity and soiled perineal region and no mortality. At 560 mg/kg, 7/10 rats died. They also showed

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SUMMARY OF HAZARD IDENTIFICATION:	
	extension of posterior paws, cyanosis, congested lungs, congested or hemorrhagic stomachs with necrotic glandular cell necrosis in the mucosa, thymus with red spots and intestines filled with bloody mucus. At 1300 mg/kg, 10/10 rats died. They also showed in addition to those seen at 570 mg/kg tremors and hypothermia. By the intravenous route, the doses were 32, 47, 68 and 100 mg/kg. At 32 mg/kg, the site of injection was discolored; there were no deaths. At 47 mg/kg, the tail injection site was necrotic. Other signs were ventral lying position, unsteady gait, pedaling movements with the hind limbs, spreading hind limbs, jumping, jerky breathing, tachynpea, dyspnea, muscle weakness and blood at the nose and in the urine; 3/30 rats died. Similar results were seen at 100 mg/kg whereby all animals died within 6 minutes. Tail necrosis was not observed due to the rapid onset of death. In the dog, the oral doses were 32, 100 and 320 mg/kg in the acute toxicity study. No toxicity was seen at 32 mg/kg; At 100 and 320 mg/kg, emesis and diarrhea were observed. Due to the emesis, higher oral doses were not pursued.
Repeated Dose Toxicity (Chronic Toxicity)	Multidose oral toxicity studies of 4- and 13- weeks were conducted in rats and dogs. In a 4-week oral toxicity study of levocetirizine and S-cetirizine in rats with a 4-week recovery period, the doses were 25, 75 and 225 mg/kg for both compounds, body weight gained were seen with both HD compounds (levocetirizine, -31%; Scetirizine, -27%). Hematological and clinical chemistry changes seen with both compounds were not treatment related, since they were not seen in the 13-week oral toxicity study. In males, both levocetirizine and S-cetirizine at the MD and HD induced enzyme induction as evidence by increased liver weight, hepatic centrilobular and midzonal enlargement and increased hepatic levels of microsomal protein, cytochrome P450, ethylmorphine N-demethylase and p-nitroanisole O- demethylase and of 7- ethoxyresorufin O-deethylase; at the lowest dose, levocetirizine also increased levels of 7-ethoxyresorufin O-deethylase, and S-cetirizine also increased levels of cytochrome P450. In males, both compounds produced hepatic centrilobular and midzonal fat and vacuolation. Levocetirizine also produced increased fat deposits in the renal cortical tubules which was not treatment related since this histopathology was not seen in the 13 week studies. All these changes were reversible. The liver was the target organ which showed enzyme induction, hepatic centrilobular and midzonal fat and vacuolation. Enzyme induction i not clinically relevant. These findings seen with levocetirizine and S-cetirizine were similar to those seen with cetirizine. A 13-week oral toxicity study was conducted with levocetirizine in rats wit a 4-week recovery period; the doses were 4, 8, 25 and 75 mg/kg. The only clinical sign was salivation. The increase in urinary protein (+31% in females and +48% in males) was not treatment related since it was not confirmed in a second 13-week oral toxicity study. Histologically, only males were affected as there was a reversible increase in the incidence of central lobular vacuolation and central lobular hypertrophy at the 25 and 75

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SUMMARY OF HAZARD IDENTIFICATION:	
	mg/kg and an increased incidence of central fat deposition at 75 mg/kg. In males, there was an increase in enzyme induction of cytochrome P-450, aniline hydroxylase, βNitroanisole O- demethylase, ethylmorphine N-demethylase and 7-Ethoxyresorufin Odeethylase in males. The liver was the target organ which showed enzyme induction, hepatic centrilobular and midzonal fat and vacuolation. The changes were reversible. Enzyme induction is not toxicologically relevant. These findings seen with levocetirizine were similar to those seen with cetirizine indicating a similar toxicity profile for both compounds. A 13-week oral toxicity study was conducted with levocetirizine and cetirizine in rats with a 4-week recovery period. The doses were 18.7, 37.5 and 75 mg/kg for levocetirizine and 37.5 and 75 mg/kg for cetirizine. Both compounds had no effect on the imunoglobulins, IgA, IgG and IgM, and lymphocyte subsets. Histologically, both compounds produced in males a reversible increase in the incidence of hepatic central lobular hypertrophy and central fat deposition. This confirms the hepatic fat deposition seen with cetirizine in the 2-year carcinogenicity study. The overall toxicity profile for both compounds was similar in rats. In dogs, a 4-week oral toxicity was conducted with levocetirizine and S-cetirizine using doses of 15, 45 and 135 mg/kg. The 135 mg/kg dose of levocetirizine was toxic requiring 1 male and 2 females to be killed on days 1, 8 and 9 in a moribund condition. On day 9 the dose was lowered to 90 mg/kg. Among the toxic symptoms seen in these animals were tremors, fecal impaction, hypothermia, abnormal gait and elevated enzymes. Both compounds were emetogenic at the MD and HD. The HD-levocetirizine treated males showed a 50% increase in urine volume. This was not seen in another 4-week study at the same dose. Other than emesis in the lower dosed animals for both compounds, no other toxicity. The target organ was the gastrointestinal tract. Levocetirizine was more toxic than S-cetirizine In a second 4-week oral toxicity study with a 4-week recovery period, cetirizine was tested along with levocetirizine and S-cetirizine. The oral doses were 33.75, 67.5 and 135 mg/kg for levocetirizine and S-cetirizine and 135 mg/kg for cetirizine. Due to severe toxicity, two 135 mg/kg levocetirizine treated animals were killed in a moribund condition, one on day 9 and the other on day 17. One cetirizine treated dog was killed in a moribund condition on day 9. On days 11 day 18, the dose of levocetirizine and cetirizine was lowered 90 mg/kg. The toxicity for the HD levocetirizine and cetirizine were similar, i.e., emesis, tremors and fecal impaction. The HD for S-cetirizine produced a toxicity profile similar to levocetirizine although not severe enough to lower the dose. Emesis was seen in all doses of the levocetirizine, S-cetirizine and cetirizine treated animals. Levocetirizine at the HD in males produced an increase in the Qtc by 15%. This was not confirmed in the first oral 4-week study at the same dose. In two 13-week studies discussed below, where the HD was lower (75 mg/kg vs. 135/90 mg/kg), there was no increase in the Qtc in the first study and in

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SUMMARY OF HAZARD IDENTIFICATION:	
	the second study there was at 13-weeks a 7% increase in the Qtc in females of both levocetirizine and cetirizine treated dogs. This slight increase is not considered toxicologically significant. The HD female with levocetirizine showed a 93% increase in eosinophils. This was not confirmed at the same dose in another 4- week toxicity study. Fecal impaction was seen 2/6 in the 37.5 mg/kg and 135/90 mg/kg levocetirizine treated animals and in 2/5 animals in the 135/90 mg/kg cetirizine group. Histology showed mucosal atrophy of the trachea in 2/3 male dogs in the 135/90 mg/kg levocetirizine treated animals. This was not confirmed in another 4- week oral study. A 13-week oral toxicity in dogs was conducted with levocetirizine; the doses were 8, 25 and 75 mg/kg. Emesis occurred in all doses in females and at the HD in males. EKG, hematological, urinary and clinical chemistry changes were not seen in another 13-week oral study. Absolute spleen weight was increased at MD and HD mg/kg which was not supported by histopathology or confirmed in another 13-week study. There were no histopathological findings. A second 13-week oral toxicity study was conducted with levocetirizine and cetirizine with a 4-week recovery period. The oral doses were 37.5 and 75 mg/kg for levocetirizine and 75 mg/kg for cetirizine. Emesis was seen with cetirizine and both doses of levocetirizine. Changes in the hematology and clinical chemistry and increased salivary weight were not confirmed in another 13-week study. Histologically, cetirizine at 75 mg/kg reduced spermatogenesis in males and produced inflammatory cells in the livers of females. Levocetirizine at 75 mg/kg produced increased small aggregates in Kupffler cells in the livers of HD females and at both doses in both sexes increased the incidence of inflammatory cells in the livers. These were not seen in another 13-week study. The toxicity profiles of cetirizine and levocetirizine are similar, and the target organ was the gastrointestinal tract.
Carcinogenicity	No carcinogenicity studies have been performed with Levocetirizine. However, evaluation of cetirizine carcinogenicity studies is relevant for determination of the carcinogenic potential of Levocetirizine. In a 2-year carcinogenicity study, in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 40, 40, 25, and 10 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years, and children 6 months to 2 years of age, respectively, on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign hepatic tumors in males at a dietary dose of 16 mg/kg (approximately 15, 15, 9, and 5 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years, and children 6 months to 2 years of age, respectively, on a mg/m^2 basis). No increased incidence of benign tumors was observed at a dietary dose of 4 mg/kg (approximately 4, 4, 2, and 1 times the MRHDs in adults, children 6 to 11 years of age, children 2 to 5 years, and children 6 months to 2 years of age, respectively on a mg/m^2 basis). The clinical significance of these findings during long-term use of Levocetirizine dihydrochloride is not known.

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SUMMARY OF HAZARD IDENTIFICATION:	
In vivo/In vitro Genotoxicity Studies	**Levocetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and in vivo micronucleus test in mice.** Levocetirizine was not mutagenic in two Reverse Bacterial Mutation Assays and not genotoxic in two Mouse Lymphoma Assays and one Micronucleus Assay. Lymphocyte Aberration assays were conducted. The first assay involved 2 tests in the absence and presence of S9. In the absence of S9, three studies were conducted. In the first study (116, 179 and 275 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the test was invalid since the Mitotic Index was increased at the highest concentration by 63%. In the second study (168, 240 and 343 ug/ml, exposure time, 20 hr; harvest time, 0 hr), levocetirizine was positive, and the Mitotic Index was increased at the highest concentration by 37%.(The positive finding was not confirmed in the third assay, test No. 3, 300, 550, 600 and 650 ug/ml). A third test (240 ug/ml, exposure time, 3 hr; harvest time, 41 hr) was invalid since a positive control was not tested. In the first study involving the presence of S9, (275, 423 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr), levocetirizine was negative at all concentrations and the results acceptable since the Mitotic Index was inhibited by 58% at the highest concentration. In the second study (240, 343 and 490 ug/ml, exposure time, 3 hr; harvest time, 17 hr), levocetirizine was negative at all concentrations. The Mitotic Index at the highest concentration was decreased by 64%. A third study (490 ug/ml, exposure time, 3 hr; harvest time, 41 hr) was invalid since a positive control was not included in the assay. The second assay involved 2 tests in the absence and presence of S9. In the absence of S9, three studies were conducted. In the first study (38, 150 and 350 ug/ml, exposure time, 24 hr; harvest time, 0 hr), levocetirizine was positive at the highest concentration. The Mitotic Index at the highest concentration was decreased by 47%. The positive results were confirmed following reexamination of the slides by an outside laboratory. In the second study (150, 350 and 500 ug/ml, exposure time, 24 hr; harvest time, 0 hr), levocetirizine was negative at all concentrations, thereby not confirming the positive results in the first study. The Mitotic Index at the highest concentration was decreased by 55%. In the third study (39, 156 and 313 ug/ml, exposure time, 48 hr; harvest time, 0 hr) was invalid since a positive control was not tested. In the presence of S9, two studies were conducted. Both studies involved exposure time, 3 hr; harvest time, 21 hr. The concentrations were 78, and 63 and 625 in the first study and 78, 400 and 800 ug/ml and their respective inhibition of Mitotic Index was -75% and 60%. Positive results were seen at 625 ug/ml in the first test and 800 ug/ml in the second test. At lower concentrations, Levocetirizine was negative. The slides from the 800 ug/ml concentration when reexamined by an outside laboratory confirmed the positive activity. However, these positive results occurred

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SUMMARY OF HAZARD IDENTIFICATION:	
	at high cytotoxic concentrations. At the lower concentrations, these results were negative indicating that levocetirizine was negative. The third assay involved 2 studies both in the absence and presence of S9. In the two studies in the absence of S9 and the two studies in the presence of S9 which were valid studies, levocetirizine was negative at all concentrations. In the two studies in the absence of S9, the parameters were first study: 600, 650, and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 44%; second study: 300, 550, 600 and 650 ug/ml, exposure time, 20 hr; harvest time, 0 hr and inhibition of the Mitotic Index at the highest concentration, 65%. In the two studies in the presence of S9, the parameters were: first study: 400, 550 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 47%; second study: 600, 650 and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, 57%. The fourth assay involved one study in the absence and one study in the presence of S9. In the absence of S9 (78, 250 and 350 ug/ml, exposure time, 20 hr; harvest time, 0 hr and increased Mitotic Index at the highest concentration, 139%), results were invalid since at the highest concentration, the Mitotic Index was enhanced and not inhibited. In the presence of S9 (60, 78, 313 and 625 ug/ml, exposure time, 3 hr; harvest time, 17 hr and inhibition of the Mitotic Index at the highest concentration, -73), levocetirizine was negative at all concentrations. The fifth assay involved 3 studies in the absence and 3 studies in the presence of S9. In the first study in the absence of S9, (116, 179 and 275 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the test was invalid since the Mitotic Index was not cytotoxic at all. In the second study (117, 168 and 240 ug/ml, exposure time, 20 hr; harvest time, 0 hr), the Mitotic Index at the highest concentration was increased (94%) rather than inhibited; the test was invalid since the Mitotic Index was not cytotoxic. In the third study (240 ug/ml, exposure time, 44 hr; harvest time, 0 hr and the Mitotic Index at the highest concentration was inhibited (65%), the test was invalid since no positive control was included in the assay. In the presence of S9, the first study (275, 423 and 650 ug/ml, exposure time, 3 hr; harvest time, 17 hr), was not valid since the Mitotic Index at the highest concentration was not cytotoxic. The second study (343, 490 and 700 ug/ml, exposure time, 3 hr; harvest time, 17 hr) was negative. The third study (240 ug/ml, exposure time, 44 hr; harvest time, 0 hr), was not valid since no positive control was used in the test. The sixth assay involved evaluation of Batches D005, D006 and D008 to determine whether there was a difference in the activity in this assay. The assay was not valid since positive controls were not included in the assay. From the results of the six assays, levocetirizine was concluded as negative in the Chromosomal aberration assay since a positive response was not confirmed in several other Chromosomal aberration assays or a

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SUMMARY OF HAZARD IDENTIFICATION:	
	positive response occurred only at a high cytotoxic concentration, and the lower concentration was negative.
Reproductive/Developmental Toxicity	In fertility and early developmental studies in rats, cetirizine was tested at oral doses up to 200 mg/kg in both sexes. Males were administered daily for 63 days before mating and through the mating period until the day before necropsy, and females were administered daily for 14 days before mating and through the mating period until 7 days of gestation. Semen was collected after copulation from the tail of the epididymis. Cetirizine did not affect sperm dynamics, male and female fertility and early fetal developmental. Embryofetal developmental studies were conducted with levocetirizine and cetirizine in rats and rabbits. In pregnant rats, oral doses of 50, 100 and 200 mg/kg of levocetirizine and 200 mg/kg of cetirizine were administered from day 6 to day 15 of gestation and sacrificed on day 20. Two rats receiving cetirizine died or were killed for humane reasons that were treatment related. Levocetirizine and cetirizine at 200 mg/kg produced an 18% and 15%, respectively, decrease in body weight gained. Levocetirizine did not produce skeletal and visceral malformations, anomalies or skeletal variants. Cetirizine did not produce skeletal and visceral malformations or anomalies. In pregnant rabbits, oral doses of 30, 60 and 120 mg/kg of levocetirizine and 120 mg/kg of cetirizine were administered from day 6 to day 18 of gestation and sacrificed on day 29. Three HD-levocetirizine treated animals died that were treatment related. Levocetirizine and cetirizine did not produce skeletal and visceral malformations. However, cetirizine produced a slight increase the incidence of skeletal variants. Fertility and reproductive performance were unaffected in male and female mice and rats that received cetirizine at oral doses up to 64 and 200 mg/kg/day, respectively (approximately 60 and 390 times the MRHD in adults on mg/m^2 basis). Available data from published literature and post marketing experience with Levocetirizine use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, birth defects, or adverse maternal or fetal outcomes. In animal reproduction studies, there **was no evidence of fetal harm** with administration of Levocetirizine by the oral route to pregnant rats and rabbits, during the period of organogenesis, at doses up to 390 times and 470 times, respectively, the maximum recommended human dose (MRHD) in adults. In rats treated during late gestation and the lactation period, cetirizine had no effects on pup development at oral doses up to approximately 60 times the MRHD in adults. In mice treated during late gestation and the lactation period, cetirizine administered by the oral route to the dams had no effects on pup development at a dose that was approximately 25 times the MRHD in adults; however, lower pup weight gain during lactation was observed at

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SUMMARY OF HAZARD IDENTIFICATION:	
	a dose that was 95 times the MRHD in adults. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. **Pre-clinical trials:** In embryo-fetal development studies, pregnant rats received daily doses of Levocetirizine up to 200 mg/kg/day from gestation days 6 to 15 and pregnant rabbits received daily doses of Levocetirizine up to 120 mg/kg/day from gestation days 6 to 18. **Levocetirizine produced no evidence of fetal harm in rats and rabbits at doses up to 390 and 470 times the MRHD,** respectively (on a mg/m^2 basis with maternal oral doses of 200 mg/kg/day and 120 mg/kg/day in rats and rabbits, respectively). No prenatal and postnatal development (PPND) studies in animals have been conducted with Levocetirizine. In a PPND study conducted in mice, cetirizine was administered at oral doses up to 96 mg/kg/day from gestation day 15 through lactation day 21. Cetirizine lowered pup body weight gain during lactation at an oral dose in dams that was approximately 95 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 96 mg/kg/day); however, there were no effects on pup weight gain at an oral dose in dams that was approximately 25 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 24 mg/kg/day). In a PPND study conducted in rats, cetirizine was administered at oral doses up to 180 mg/kg/day from gestation day 17 to lactation day 22. Cetirizine did not have any adverse effects on rat dams or offspring development at doses up to approximately 60 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 30 mg/kg/day). Cetirizine caused excessive maternal toxicity at an oral dose in dams that was approximately 350 times the MRHD (on a mg/m^2 basis with a maternal oral dose of 180 mg/kg/day). **Lactation:** There are no data on the presence of Levocetirizine in human milk, the effects on the breastfed infant, or the effects on milk production. However, cetirizine has been reported to be present in human breast milk. In mice and beagle dogs, studies indicated that cetirizine was excreted in milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Levocetirizine dihydrochloride and any potential adverse effects on the breastfed child from Levocetirizine dihydrochloride or from the underlying maternal condition. **Pre-clinical trials:** Cetirizine was detected in the milk of mice. **No adverse developmental effects on pups were seen when cetirizine was**

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SUMMARY OF HAZARD IDENTIFICATION:	
	administered orally to dams during lactation at a dose that was approximately 25 times the MRHD in adults. Studies in beagle dogs indicated that approximately 3% of the dose of cetirizine was excreted in milk. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.
Highly Sensitizing Potential	No any sensitivity to skin observed.

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 effect	**Adult dose:** 5 mg/day **Adverse effects:** Hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

NOAEL/LOAEL	NOAEL in rat: 75 mg/kg, orally in a 76-week study

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	76 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	NOAEL value is selected
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{75\text{ (NOAEL) x }50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 5}$ = 15 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Levocetirizine.
- https://pubchem.ncbi.nlm.nih.gov/compound/Levocetirizine.
- https://www.drugs.com/pro/levocetirizine.html
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022157s000PharmR.pdf
- https://www.rxlist.com/consumer_levocetirizine_xyzal/drugs-condition.htm