PERMITTED DAILY EXPOSURE FOR AMBROXOL 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 **Ambroxol Hcl** 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:

Ambroxol is a drug that breaks up phlegm, used in the treatment of respiratory diseases associated with viscid or excessive mucus. Recently, a hypothesis suggested that it may have a potential role in treatment of Paget's disease of bone, Parkinsonism, and other common diseases of aging-associated diseases involving dysfunction of autophagy. Ambroxol is often administered as an active ingredient in cough syrup.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

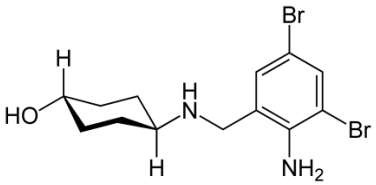
IUPAC NAME: trans-4-(2-Amino-3, 5-dibrombenzylamino)-cyclohexanol.

Chemical Abstract Services (CAS) Registry Number: 18683-91-5

Molecular Weight: 378.10 $g \cdot mol^{-1}$

Chemical Formula: $C_{13}H_{18}Br_2N_2O$

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	No specific pharmacodynamics studies were undertaken for the indication under assessment, Ambroxol hydrochloride is a well known and widely used secretolytic and secretomotoric agent used for inflammatory diseases of the respiratory tract. Hence its pharmacodynamics model is generally well known, and there are no clinically relevant pharmacodynamics issues known at this point.
Pharmacokinetic data	The pharmacokinetics of Ambroxol hydrochloride has been extensively investigated in mouse, rat, rabbit and dogs. **Absorption:** Gastrointestinal absorption of Ambroxol HCl is rapid and almost complete in all animal species tested as well as in human. The absolute oral bioavailability of Ambroxol HCl is high in human but lower in animals. **Distribution:** Consistent with its large volume of distribution, a rapid and extensive distribution of Ambroxol HCl was seen in all species examined. Ambroxol HCl is rapidly and extensively distributed from the blood into tissues. Ambroxol HCl passes the placenta. Preferential tissue distribution has been found in brain, skin, uveal tract and in the foetus. **Metabolism:** Ambroxol HCl is extensively metabolized via multiple pathways. In plasma, DBAA (3, 5 dibromoanthranilic acid) is the predominant circulating metabolite in all animal species tested as well as in human. In contrast to Ambroxol HCl, the tissue distribution of DBAA is low. Based on combined in vivo and in vitro metabolism data, the contribution of CYP3A4 to total clearance of Ambroxol HCl in human was estimated to be approximately 20%. Plasma protein binding is moderate for Ambroxol HCl but very high for its metabolite DBAA in all species tested. Ambroxol HCl is approximately evenly distributed between blood cells and plasma, while DBAA essentially does not distribute into blood cells. **Clearance:** The clearance of Ambroxol HCl ranged from moderate to high and the volume of distribution ranged from moderate to large in animals and human. Ambroxol HCl half-life was short in mouse and dog, but moderate in rat and human. **Excretion:** Ambroxol HCl is eliminated predominantly by metabolism. Urine is the predominant route of excretion of Ambroxol-derived radioactivity in human and the major route of excretion for mouse, rabbit, and dog. In rats, bile/faeces is the major route of excretion. Ambroxol HCl and DBAA are not substrates of the efflux transporter Pgp. Given that CYP3A4 contributes to only about 20% of the total clearance of Ambroxol HCl in human, the potential increase in plasma levels of Ambroxol HCl in the presence of a strong CYP3A4 is not considered to be an issue.
Acute Toxicity	Following single oral administration Ambroxol hydrochloride shows little toxicity.

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

In repeat-dose studies, oral doses of 150 mg/kg/day (mouse, 4 weeks), 50 mg/kg/day (rat, 52 and 78 weeks), 40 mg/kg/day (rabbit, 26 weeks) and 10 mg/kg/day (dog, 52 weeks) were the no-observed adverse effect level (NOAEL). No toxicological target organs were detected.

Four week intravenous toxicity studies with Ambroxol hydrochloride in rats (4, 16 and 64 mg/kg/day) and in dogs (45, 90 and 120 mg/kg/day (infusion 3 h/day)) showed no severe local and systemic toxicity including histopathology. All adverse effects were reversible.

In subchronic studies, substance related deaths and sign of toxicity, mainly in CNS, were seen in groups exposed to the highest dose. Following chronic repeated oral administration for the NOAELs were

- 100 mg/kg body wgt./day for the rat
- 40 mg/kg body wgt./day for the rabbit
- 10 mg/kg body wgt./day for the dog. No major changes were noted. High repeated doses of Ambroxol hydrochloride (250 mg/kg/day for 52 weeks) appear to affect haematological parameters and may cause degenerative renal changes in the rat. However, these changes were not observed in all chronic studies.

In the recent GLP-compliant 13 weeks toxicokinetics/toxicity studies performed in mice, rat, dogs doses with oral Ambroxol HCl up to 800, 1000 or 160 mg/kg/day, respectively, no adverse effects other than body weight decrements was observed in parameters of general toxicity. Taking into account the exposure of the more sensitive species (dog 160 mg/kg/day) and the AUC in human for maximum therapeutic dose (120 mg/day), a 20 fold safety margin can therefore be anticipated. In conclusion, repeat dose toxicology studies in different animal species indicated that Ambroxol HCl is safe for treatment of sore throat under the conditions specified in the SPC.

Organism	Test type	Route	Dose (mg/kg)	Effect	reference
Rat	Ld_{50}	Intraperitoneal	262	Behavioral: tremor; behavioral: convulsions or effect on seizure threshold; gastrointestinal: peritonitis	Oyo Yakuri. Pharmacometrics., 21(281), 1981
Rat	Ld_{50}	Subcutaneous	1489	Behavioral: somnolence (general depressed activity); behavioral: ataxia; lungs, thorax, or respiration: dyspnea	Iyakuhin Kenkyu. Study of Medical Supplies., 12(263), 1981
Rat	Ld_{50}	Intravenous	100	Behavioral: tremor; behavioral: convulsions or effect on seizure threshold	Oyo Yakuri. Pharmacometrics., 21(281), 1981
Mouse	Ld_{50}	Oral	2380	Behavioral: convulsions or effect on seizure threshold	Oyo Yakuri. Pharmacometrics., 21(281), 1981
Mouse	Ld_{50}	Intraperitoneal	268	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]

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SUMMARY OF HAZARD IDENTIFICATION:

	Mouse	Ld_{50}	Subcutaneous	1060	Behavioral: somnolence (general depressed activity); behavioral: ataxia; lungs, thorax, or respiration: dyspnea	Iyakuhin Kenkyu. Study of Medical Supplies., 12(263), 1981
	Mouse	Ld_{50}	Intravenous	138	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Dog	Ld_{50}	Oral	500	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Dog	Ld_{50}	Intraperitoneal	125	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Rabbit	Ld_{50}	Oral	2597	Gastrointestinal: ulceration or bleeding from stomach; gastrointestinal: ulceration or bleeding from duodenum; gastrointestinal: decreased motility or constipation	Oyo Yakuri. Pharmacometrics., 21(281), 1981
	Rabbit	Ldlo	Intraperitoneal	400	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Rabbit	LD_{50}	Intravenous	64	Behavioral: convulsions or effect on seizure threshold; behavioral: ataxia; lungs, thorax, or respiration: respiratory stimulation	Oyo Yakuri. Pharmacometrics., 21(281), 1981
	Guinea pig	LD_{50}	Oral	1180	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Guinea pig	LD_{50}	Intraperitoneal	280	Null	Arzneimittel-Forschung. Drug Research., 28(889), 1978 [PMID:581987]
	Rat	LD_{50}	Oral	4203	Behavioral: somnolence (general depressed activity); behavioral: ataxia; lungs, thorax, or respiration: dyspnea	Iyakuhin Kenkyu. Study of Medical Supplies., 12(263), 1981

Carcinogenicity	Ambroxol hydrochloride did not show any tumorigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg/day) and rats (65, 250 and 1000 mg/kg/day) when treated with a dietary admixture for 105 and 116 weeks, respectively.

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SUMMARY OF HAZARD IDENTIFICATION:	
In vivo/In vitro Genotoxicity Studies	Genotoxicity studies in vitro (Ames and chromosome aberration test) and in vivo (mouse micronucleus test) did not reveal any mutagenic potential of Ambroxol hydrochloride.
Reproductive/Developmental Toxicity	Ambroxol hydrochloride was neither embryotoxic nor teratogenic when tested at oral doses up to 3000 mg/kg/day in rats and up to 200 mg/kg/day in rabbits. The fertility of male and female rats was not affected up to 500 mg/kg/day. The NOAEL in the peri- and post-natal development study was 50 mg/kg/day. At 500 mg/kg/day, Ambroxol hydrochloride was slightly toxic for dams and pups, as shown by a retarded body-weight development and reduced litter size.
Highly Sensitizing Potential	Ambroxol hydrochloride as 1% solution caused no irritation to the rabbit eye or skin.

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	**Mucolytic** **Adult:** As Ambroxol hydrochloride: 30 mg tid or 60 mg bid. As extended-release cap: 75 mg once daily. **Child:** As Ambroxol hydrochloride: <2 years 7.5-15 mg bid. 2-5 years 7.5-15 mg tid; 6-12 years 15-30 mg bid or tid; >12 years Same as adult dose. **Adverse effects:** *Gastrointestinal disorders:* Nausea, vomiting, diarrhoea, dyspepsia, heartburn, dry mouth or throat, altered taste.

NOAEL/LOAEL	10 mg/kg/day (Dog, 52 weeks) were the no-observed adverse effect level (NOAEL).

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2	For extrapolation from Dogs to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	1 Year study in non-rodent (Short duration).
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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{10 (NOAEL) x 50}}{\text{2 x 10 x 10 x 1 x 5}}$ = 0.5 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Ambroxol.
- https://www.bfarm.de/SharedDocs/Downloads/EN/Drugs/vigilance/PSURs/csp/a-b/ambroxol.pdf?__blob=publicationFile&v=3.
- http://mri.cts-mrp.eu/download/BE_H_0181_001_PAR.pdf.