PERMITTED DAILY EXPOSURE FOR ACEBROPHYLLINE

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 Acebrophylline 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:

Acebrophylline, a Xanthine derivative, is prescribed as a bronchodilator for the treatment of bronchial asthma and COPD in adults. Acebrophylline alter mucus gel secretion phase by lowering viscosity and increasing the serous gel phase. By augmenting ciliary motility, Acebrophylline increases the mucociliary clearance. Acebrophylline is an airway mucus regulator with anti-inflammatory action. The drug's approach involves several points of attack in obstructive airway disease. The molecule contains Ambroxol, which facilitates various steps in the biosynthesis of pulmonary surfactant, theophylline-7 acetic acid whose carrier function raises blood levels of Ambroxol, thus rapidly and intensely stimulating surfactant production. The resulting reduction in the viscosity and adhesivity of the mucus greatly improves ciliary clearance.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

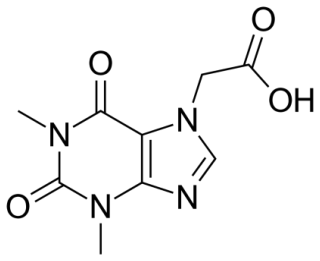
IUPAC NAME: 4-[(2-amino-3, 5-dibromophenyl) methylamino] cyclohexan-1-ol; 2-(1, 3-dimethyl-2, 6-dioxopurin-7-yl) acetic acid.

Chemical Abstract Services (CAS) Registry Number: 96989-76-3

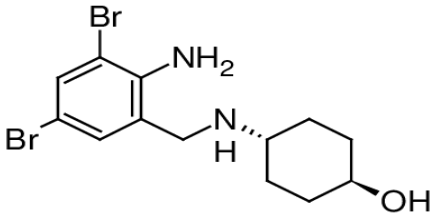
Molecular Weight: 616.30292 g/mol

Chemical Formula: $C_{22}H_{28}Br_2N6O5$

Molecular Structure: Compound is made of 02 components



Acefylline



Ambroxol

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4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics Data	Acebrophylline inhibits intracellular phosphodiesterase associated with Camp levels and facilitates bronchial muscles relaxation. Acebrophylline selectively inhibits phosphatidylcholine and phospholipase A, TNF-alpha and leukotrienes. Inhibition of such pro-inflammatory mediators can significantly reduce the airway inflammation and obstruction in chronic stages.
Pharmacokinetic Data	In healthy volunteers, given 200 mg oral Acebrophylline, the two components of the molecule - Ambroxol and theophylline-7 acetic acid are released in the stomach and absorbed there and in the intestine, reaching optimal concentrations of Ambroxol and very low levels of theophylline-7 acetic acid. Ambroxol reaches its peak in serum (mean Cmax 0.369 mcg/mL) at 2 hrs and theophylline- 7 acetic acid after 1 hr (mean Cmax 0.008 mcg/mL). Thus it appears that the latter is either poorly absorbed or metabolised very fast and is eliminated in a fairly short time. Its low blood levels mean it is not likely to cause the untoward effects seen in man after theophylline, whose therapeutic window corresponds to much higher plasma concentrations (10-20 mcg/mL) [35, 36] (fig. 5). Another factor in the excellent tolerability of acebrophylline is its pulmonary tropism [37]. The low plasma levels of the xanthine derivative are a further guarantee that there should be no interference with any other theophylline-based drug that might be used concomitantly. Its stability in an acid environment, excellent tissue diffusion and fairly long half-life mean that Acebrophylline need only be taken twice a day.
Acute Toxicity	**Acute toxic effects:** Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.
Repeated Dose Toxicity (Chronic Toxicity)	**Study 1:** Milvio *et al.*, in a study, treated 41 patients between 30 and 80 years old, with acute or asthma-like bronchitis or flare-ups of chronic forms, with or without fever, increased bronchial secretion, cough and mucous, mucopurulent or purulent sputum. Patients were randomized to receive Acebrophylline (100 mg b.i.d.) for 20 days. At the end of this period there was a significant decrease in the amount of sputum in both groups; viscosity was also greatly reduced especially in the patients

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)	given Acebrophylline. **Study 2:** Two early clinical trials compared the effectiveness of Acebrophylline and Ambroxol. Milvio *et al.*, in a double-blinded study, treated 41 patients between 30 and 80 years old, with acute or asthma-like bronchitis or flare-ups of chronic forms, with or without fever, increased bronchial secretion, cough and mucous, mucopurulent or purulent sputum. Patients were randomised to receive Acebrophylline or Ambroxol (both at 100 mg b.i.d.) for 20 days. At the end of this period there was a significant decrease in the amount of sputum in both groups; viscosity was also greatly reduced especially in the patients given Acebrophylline. The two treatments relieved clinical symptoms similarly, but acebrophylline increased FEV1 by about 16%, significantly more than Ambroxol. Fracchia *et al.* reported similar results from their controlled trial comparing Acebrophylline (100 mg b.i.d.) and ambroxol (30 mg t.i.d.) in 38 patients with COLD, mean age 64.8 years. The two compounds gave similar improvements in mucous visco-elasticity, making it more fluid and easier to expel; this resulted in an improvement – already evident from the third day of treatment – in subjective and objective symptoms compared to baseline. However, after 14 days of treatment, only the patients assigned to Acebrophylline showed a statistically significant increase of FEV1 and VC and a reduction of airway resistance (Raw) (fig. 8). Similar findings come from subsequent studies on larger caselists. Catena *et al*., in a multicentre, randomised, parallelgroups trial, enrolled 122 patients, mean age 54.6 years, with stable asthma-like chronic bronchitis, FEV1 between 50% and 80% of the expected value, and a positive broncho-reversibility test. Of these, 60 were treated with Ambroxol (one 30-mg sachet t.i.d.), and the other 62 received Acebrophylline (one 100-mg sachet b.i.d.) for 45 days. Acebrophylline was more active than ambroxol, in relieving clinical signs and symptoms (amount and appearance of sputum, pathological auscultation and dyspnea) and improving respirato- ry function (VC, FEV1 and forced expiratory flow, FEF25-75) indicative of relief of obstruction; acebrophylline's action was significantly superior to that of ambroxol, as a result of the stronger stimulation of pulmonary surfactant production and more effective mucoregulation. Acebrophylline also significantly reduced the frequency of bronchospastic attacks, the difference reaching significance between 15 and 30 days of treatment; during this period 21% of patients in the Acebrophylline group and 54% taking ambroxol had at least one episode of bronchoconstriction. The picture improved further between 30 and 45 days of treatment, when the figures were respectively 5% and 44%. The mean number of bronchospastic episodes was also significantly lower in the Acebrophylline patients (tables 4 and 5). Much the same findings were reported from a multicentre, non-controlled trial in 84 patients with asthma-like
Repeated Dose Toxicity (Chronic Toxicity)	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:	
	bronchitis given acebrophylline for 60 consecutive days. In children with asthma-like bronchitis, acebrophylline was compared with ambroxol or a virtual placebo (multivitamin preparation), and the findings were similar to those in adults with the same illness. Fiocchi *et al.* [48] investigated 30 children with asthma-like bronchitis, aged 2-4 years; one group (16 patients) was given acebrophylline, 5 mL/day (50 mg), divided in two doses/day, and the other 14 patients were given 9 mL/day ambroxol (27 mg), in three doses/day. The children were treated for 21 days, followed by two weeks' follow-up. Patients given Acebrophylline experienced more prompt and more marked protection against bronchospasm than those given the ambroxol group. This was already evident from the first week, and was particularly striking in the last week of treatment (14-21 days), when none of the 16 children given Acebrophylline suffered bronchospasm, compared to six in the ambroxol group (fig. 9). This improvement was reflected in the reduced need for â2-agonists which was more marked in the Acebrophylline group (table 6). Relief of symptoms, particularly those linked to the bronchospasm, was also different in the two groups. Acebrophylline acted sooner than ambroxol to improve pathological auscultation findings and relieve cough. Another trial in 40 children with infectious asthma, treated with Acebrophylline or placebo for 21 days, confirmed these findings.
Carcinogenicity	IARC: Not classified. NTP: Not listed. OSHA: Not listed.
In vivo/In vitro Genotoxicity Studies	No data available
Reproductive/Developmental Toxicity	No data available
Highly Sensitizing Potential	Skin contact may result in inflammation characterized by itching, scaling, reddening, blistering, pain or dryness. Eye contact may result in redness, pain or severe eye damage. Inhalation may cause irritation of the lungs and respiratory system. Overexposure may result in serious illness or death.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No available
Clinical therapeutic and adverse effects	For COPD and bronchial asthma (Adults): Consider administration of 100 mg of Acebrophylline, twice daily. **Adverse Effects:** Acebrophylline can cause glycosuria, epigastric pain, low blood pressure, GI discomfort or distension, anorexia, drowsiness, breathing difficulties, albuminuria, hyperglycemia, leucocytosis, mild skin reactions, fever,

	fatigue and nasal inflammation.

NOAEL/LOAEL	4 mg/kg/day NOAEL value selected

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	No data available
F2: Inter Individual Variability	10	Used for differences between individuals in the human population
F3: Duration of Toxicity	10	20 days study available (short duration).
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	1	NOAEL value is selected
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

5. CALCULATION:

$$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$$

PDE Calculation = 4 (NOAEL) x 50
1 x 10 x 10 x 1 x 1
= 2 mg/day

6. REFERENCES:

- http://www.drugsupdate.com/generic/view/1114/Acebrophylline
- https://www.researchgate.net/publication/323912454
- https://medsafe.govt.nz/profs/class/Agendas/agen53Bilastine.pdf
- https://www.ncbi.nlm.nih.gov/pubmed/22616813
- https://www.drugbank.ca/drugs/DB11591
- https://aksci.com/sds/W0001_SDS.pdf

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