PERMITTED DAILY EXPOSURE FOR MEBEVERINE

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 Mebeverine 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:

Mebeverine is a drug used to alleviate some of the symptoms of irritable bowel syndrome. It works by relaxing the muscles in and around the gut.

It has not been tested in pregnant women nor in pregnant animals so pregnant women should not take it; it is expressed at low levels in breast milk, while no adverse effects have been reported in infants, breastfeeding women should not take this drug.

Adverse effects include hypersensitivity reactions and allergic reactions, immune system disorders, skin disorders including hives, edema and widespread rashes.

Additionally, the following adverse effects have been reported: heartburn, indigestion, tiredness, diarrhea, constipation, loss of appetite, general malaise, dizziness, insomnia, headache, and decreased pulse rate.

It does not have systemic anticholinergic side effects.

Mebeverine can, on highly rare occasions, cause drug-induced acute angle closure glaucoma.

Mebeverine is an anticholinergic but its mechanism of action is not known; it appears to work directly on smooth muscle within the gastrointestinal tract and may have an anesthetic effect, may affect calcium channels, and may ‘ affect muscarinic receptors.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

It is a white to almost white, crystalline powder having a very bitter taste, very soluble in water, freely soluble in ethanol and practically insoluble in ether.

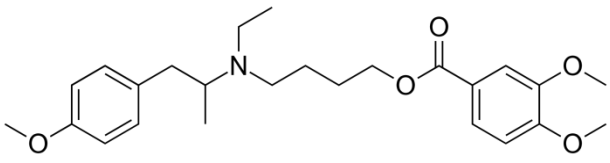
IUPAC name: (RS)-4-(Ethyl[1-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate

Chemical Abstract Services (CAS) Registry Number: 2753-45-9

Molecular Weight: 429.6 g/mol g·mol−1

Chemical Formula: $C_{25}H_{35}NO_5$

Molecular Structure:



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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	Mechanism of Action Mebeverine has a direct non-specific relaxant effect on vascular, cardiac, and other smooth muscle. Studies indicate that the spasmolytic activity of mebeverine is not restricted to one particular system, but the compound possesses a polyvalent spasmolytic action in which at least three types of mechanisms are involved: • a direct musculotropic action involving calcium ion exchange and stabilization of excitable membranes; • a competitive antimuscarinic activity of about 0.05 - 0.1 times that of atropine; • a local anaesthetic activity together with potentiation of sympathetic inhibitory influences due to blockade of noradrenaline uptake into sympathetic nerve endings. In in vitro studies mebeverine hydrochloride has been shown to have a papaverine-like spasmolytic effect on the smooth muscle of the ileum, uterus and the gall bladder. It possesses a strong local anaesthetic activity. When tested in vivo in various species, mebeverine hydrochloride was found to be three to five times more powerful than papaverine in blocking spasm of smooth muscle and in relieving the carbachol-induced spasm of the sphincter of Oddi in rabbits, mebeverine hydrochloride proved to be twenty times more active than papaverine. In vivo studies also demonstrate that mebeverine has only minor effects on normal intestinal peristalsis but possesses spasmolytic activity when hypermotility is induced. The spasmolytic activity is found in all parts of the gastrointestinal tract and, in some experiments, has been found to be more active on colonic smooth muscle. Studies with mebeverine hydrochloride 100 mg tablets indicate that mebeverine is free of central anticholinergic effects, and practically free of peripheral effects with an activity of less than 0.001 times that of atropine. Mebeverine does not show central depressant or analgesic effects, and only in high doses are some central stimulating effects observed. No ganglion blocking or interference with neuromuscular transmission occurs. Mebeverine injected intravenously in animals produces transient cardiac arrhythmias, bradycardia and ECG changes.
Pharmacokinetics data	**Absorption**: Following oral administration of 3H and 14C labelled Mebeverine hydrochloride in man, absorption was followed by the appearance in the plasma of veratric acid and an oxidised metabolite of the Mebeverine alcohol moiety of the drug, Mebeverine acid. **Distribution:** Maximum plasma radioactivity levels were found 1-3 hours after dosing. Binding of Mebeverine to human serum albumin was 75%. Metabolism The primary metabolic step in Mebeverine degradation is hydrolysis of the ester function.

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SUMMARY OF HAZARD IDENTIFICATION:

Excretion: The major route of excretion of the metabolites is via the urine (95%) and the peak rate of excretion usually occurs within two hours. Virtually 98% urinary recovery of the conjugated and unconjugated metabolites was observed after a period of 24 hours. No unchanged Mebeverine was excreted with the urine.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Rat	LD50	Oral	1540	Null	German Offenlegungsschrift Patent Document., #2821584
Rat	LD50	Intravenous	17.7	Null	German Offenlegungsschrift Patent Document., #2821584
Mouse	LD50	Intraperitoneal	150	Null	Psychotropic Drugs and Related Compounds, 2nd ed., Usdin, E., and D.H. Efron, Washington, DC, 1972, -(338), 1972

Repeated Dose Toxicity (Chronic Toxicity)

Effects in repeat-dose toxicity studies, after oral and parenteral doses, were indicative of central nervous involvement with behavioral excitation, mainly tremor and convulsions. In the dog, the most sensitive species, these effects were seen at oral doses equivalent to 3 times the maximum recommended clinical dose of 400 mg/day based on body surface area (mg/m^2) comparisons.

Carcinogenicity

No carcinogenicity studies have been performed.

In vivo/In vitro Genotoxicity Studies

In conventional in vitro and in vivo Genotoxicity tests Mebeverine was devoid of genotoxic effects.

Reproductive/Developmental Toxicity

Pregnancy: There are no or limited amount of data from the use of Mebeverine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Mebeverine is not recommended during pregnancy.
Lactation: It is unknown whether Mebeverine or its metabolites are excreted in human milk. The excretion of Mebeverine in milk has not been studied in animals. Mebeverine should not be used during breast-feeding.
Fertility: There are no clinical data on male or female fertility; however, animal studies do not indicate harmful effects of Mebeverine.

However, embryotoxic effects (reduction in litter size, increased incidence of resorption) were noticed in rats at doses equivalent to twice the maximum daily clinical dose. This effect was not observed in rabbits. No effects on male or female fertility were noted in rats at doses equivalent to the maximum clinical dose.

Pregnancy Category: B2 Safe use in pregnancy has not been established relative to adverse effects on foetal development. Therefore, Mebeverine tablets are not recommended during the first trimester of pregnancy and otherwise risk-benefit must be considered in its use in pregnant women.
Teratogenicity has not been demonstrated in teratology studies in rats and rabbits

Highly Sensitizing Potential

In very rare cases allergic reactions have been reported, in particular, hypersensitivity, urticaria, angioedema, face oedema and exanthem.

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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	**Clinical therapeutic dose:** The recommended adult dose is one Mebeverine hydrochloride 135 mg (1 tablet) three times daily, preferably before or with food. In case one or more doses are missed, the patient should continue with the next dose as prescribed, the missed doses are not to be taken in addition to the regular dose. After a period of several weeks when the desired effect has been obtained, the dosage may be gradually reduced. **Adverse effects:** Because of the low incidence of adverse drug effects reported a meaningful estimate of adverse reactions is difficult to obtain. The following side effects have been reported in clinical studies: Indigestion, heartburn, dizziness, insomnia, anorexia, headache, decrease in pulse rate, constipation, general malaise.

NOAEL/LOAEL	Minimum therapeutic dose (2.7 mg/kg/day) has been selected as the NOAEL value.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	As NOAEL value has been taken from smallest therapeutic dose hence extrapolation need not required.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	Exact data not available hence worst condition considered.
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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{2.7 (NOAEL) x 50}}{\text{1 x 10 x 10 x 1 x 5}}$ = 0.27 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Mebeverine
- https://medicines.org.au/files/gopcolof.pdf
- https://pubchem.ncbi.nlm.nih.gov/compound/Mebeverine-hydrochloride
- https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PPA1151-122-001_11112013131108.pdf
- https://www.medicines.org.uk/emc/product/2315/smpc