PERMITTED DAILY EXPOSURE FOR ACECLOFENAC

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 Aceclofenac 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:

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) analog of Diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Aceclofenac is practically insoluble in water with good permeability. It is metabolized in human hepatocytes and human microsomes to form [2-(2', 6'-dichloro-4'-hydroxy- phenylamino) phenyl] acetoxyacetic acid as the major metabolite, which is then further conjugated. Aceclofenac falls under the BCS Class II, poorly soluble and highly permeable drug. Aceclofenac works by inhibiting the action of cyclooxygenase (COX) that is involved in the production of prostaglandins (PG) which is accountable for pain, ‘swelling, inflammation and fever.

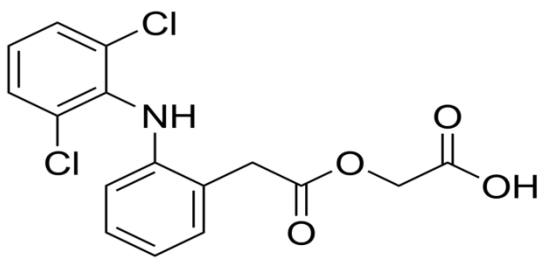
IUPAC Name: 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid

Chemical Abstract Services (CAS) Registry Number: 89796-99-6.

Molecular Weight: 353.02161 g/mol g·mol−1

Chemical Formula: C16H13Cl2NO4

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	Aceclofenac is a NSAID that inhibits both isoforms of COX enzyme, a key enzyme involved in the inflammatory cascade. COX-1 enzyme is a constitutive enzyme involved in prostacyclin production and protective functions of gastric mucosa whereas COX-2 is an inducible enzyme involved in the production of inflammatory mediators in response to inflammatory stimuli. Aceclofenac displays more selectivity towards COX-2 (IC50 of 0.77uM) than COX-1 (IC50 of >100uM), which promotes its gastric tolerance compared to other NSAIDs. The primary metabolite, 4'-hydroxyaceclofenac, also minimally inhibits COX-2 with IC50 value of 36uM. Although the mode of action of Aceclofenac is thought to mainly arise from the inhibition of synthesis of prostaglandins (PGE2), Aceclofenac also inhibits the production of inflammatory cytokines, interleukins (IL-1β, IL-6), and tumor necrosis factors (TNF). It is also reported that Aceclofenac also affects the cell adhesion molecules from neutrophils. Aceclofenac also targets the synthesis of glycosaminoglycan and mediates chrondroprotective effects.
Pharmacokinetic Data	**Absorption:** Aceclofenac is rapidly and completely absorbed from the gastrointestinal tract and circulates mainly as unchanged drug following oral administration. Peak plasma concentrations are reached around 1.25 to 3 hours post-ingestion, and the drug penetrates into the synovial fluid where the concentration may reach up to 60% of that in the plasma. There is no accumulation in regular dosing, with similar maximum plasma concentration (Cmax) and time to reach peak plasma concentration (Tmax) after single and multiple doses. **Route of Elimination:** The main route of elimination is via the urine where the elimination accounts for 70-80% of clearance of the drug. Approximately two thirds of the administered dose is excreted via the urine, mainly as glucuronidated and hydroxylated forms of Aceclofenac. About 20% of the dose is excreted into feces. **Volume of Distribution:**

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:	
	The volume of distribution is approximately 25 L.
Acute Toxicity	Organism Test type Route Dose (mg/kg) Effect Reference Women TDLo Oral 20 Vascular: strictira; cjamges om vessels; lungs, thorax, or respiration: sputum; skin and appendages (skin): dermatitis, allergic: after systemic exposure Annals of Pharmacotherapy., 29(1168), 1995 Rat LD50 Oral 130 Null Arzneimittel-Forschung. Drug Research., 41(1265), 1991 [PMID:1815528]
Repeated Dose Toxicity (Chronic Toxicity)	No data available.
Carcinogenicity	Carcinogenicity studies in the mouse (systemic exposure to Aceclofenac unknown) and in the rat (metabolism to Diclofenac) did not show any carcinogenic effect.
Genotoxicity	In vivo/In vitro Genotoxicity Studies Aceclofenac was negative in genotoxicity tests.
Reproductive/Development Toxicity	There is no information on the use of Aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastroschisis after use of prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Aceclofenac should not be given unless clearly necessary. If Aceclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses. inhibition of uterine contractions

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SUMMARY OF HAZARD IDENTIFICATION:

	resulting in delayed or prolonged labour. Consequently, Aceclofenac is contraindicated during the third trimester of Pregnancy. **Lactation** There is no information on the secretion of Aceclofenac to breast milk; there was however no notable transfer of radio labelled (14C) Aceclofenac to the milk of lactating rats. The use of Aceclofenac should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus. **Fertility** The use of Aceclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Aceclofenac 100 mg Film-coated Tablets should be considered. Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with Aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some foetuses.
Highly Sensitizing Potential	Highly Sensitizing Potential As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

IDENTIFICATION OF CRITICAL EFFECTS:

Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	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 and adverse effects The recommended dose is 200 mg daily, taken as 2 separate 100 mg daily, one tablet in the morning & one tablet in the evening. Adverse Effects: Some common adverse effects include gastro-intestinal disorders (dyspepsia, abdominal pain, nausea), rash, ruber, urticaria, symptoms of enuresis, headache, dizziness, and drowsiness. NOAEL/LOAEL

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NOAEL/LOAEL	(2 mg/kg/day) Minimum therapeutic dose is considered as NOAEL.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	Minimum therapeutic dose considered.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity	10	(Repeat Dose Toxicity) 10 No data available.
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	

5. CALCULATION:

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

PDE Calculation = $\frac{2 \text{ (NOAEL)} \times 50}{1 \times 10 \times 10 \times 1 \times 5}$

= 0.2 mg/day

6. REFERENCES:

- https://pubchem.ncbi.nlm.nih.gov/compound/Aceclofenac.
- http://www.e-lactancia.org/media/papers/DS-Aceclofenac-2007_1.pdf.
- https://www.medicines.org.uk/emc/product/2389/smpc.
- http://mri.cts-mrp.eu/download/BE_H_0133_001_FinalSPC.pdf