PERMITTED DAILY EXPOSURE FOR FEBUXOSTAT

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 Febuxostat 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:

3. IDENTITY OF THE ACTIVE SUBSTANCE:

IUPAC name:

Chemical Abstract Services (CAS) Registry Number:

Molecular Weight:

Chemical Formula:

Molecular Structure:

4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Febuxostat is a potent xanthine oxidase inhibitor that was approved for the treatment of chronic Hyperuricaemia and gout. It is of a different chemical class than allopurinol and a more selective inhibitor of enzyme activity. In both in vitro and in vivo animal studies, Febuxostat inhibited XO more potently than allopurinol. Animal studies have demonstrated that the potency of Febuxostat is 10–30 times that of allopurinol. In one study in chimpanzees (which resemble humans in lacking uricase and having higher purine metabolite levels and urate excretion rates), both allopurinol and Febuxostat (each 5 mg/kg/day orally), decreased serum urate levels after 24, 48, and 72 hours of administration. However, Febuxostat was more effective than allopurinol at lowering uric acid. Allopurinol decreased serum urate concentration by 28% (24 h), 42% (48 h), and 45% (72 h), as

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	compared with the respective values for Febuxostat of 56%, 70% and 74%.
Pharmacokinetics data	Febuxostat was rapidly absorbed from the gastrointestinal tract following oral administration of Febuxostat to mice (tmax 0.5-2 h), rats and dogs (tmax 0.25-0.5 hours). Plasma total radioactivity AUC values were generally 6-7-fold higher in mice and rats than those in dogs given an equivalent dose. Febuxostat AUC values were nearly 9 times higher in rats than in dogs. The terminal half-life of Febuxostat generally ranged from 2-4 hours in mice and appeared to be slightly longer in rats and dogs. Absorption was decreased 36-48% in rats and 55% in dogs when Febuxostat was administered with food. In vitro and ex vivo plasma protein binding studies with Febuxostat showed that the drug is highly bound in rat plasma (≥98.8%). The studies showed that Febuxostat is widely distributed to most tissues and organs. Following administration of Febuxostat to mice, rats and dogs, metabolic profiles in plasma and urine appeared to be qualitatively similar between the species. Febuxostat was the major component found in the plasma of all species studied. Several metabolites were present at relatively lower concentrations in all species. Following either i.v. or p.o. administration of Febuxostat to mice, rats or dogs, faecal excretion was generally the main route of elimination (especially in dogs).
Acute Toxicity	Febuxostat does not pose an acute toxicity hazard by the oral route based on studies performed in rats (lethal dose 300-600 mg/kg) and dogs (no deaths up to 2000 mg/kg).
Repeated Dose Toxicity (Chronic Toxicity)	**NON-CLINICAL STUDIES** **Study 1:** In rats and consequent to the Histopathological changes at 48 mg/kg/day (31x human plasma exposure at 80 mg/day), various serum chemistry parameters (increased BUN, creatinine, phospholipids, triglycerides), hematology parameters (increased leukocytes, decreased erythrocytes) and urinalysis parameters (increased excretion of potassium and sodium) were altered. **The no observed adverse effect level (NOAEL) for 26-week rat study was considered to be 12 mg/kg/day (8x plasma exposure at 80 mg/day).** In dogs, less significant changes in serum chemistry, hematology and urinalysis parameters were observed at 45 mg/kg/day (55x plasma exposure at 80 mg/day). **The NOAEL for 52-week dog study was considered to be 5 mg/kg/day (0.5x plasma exposure at 80 mg/day).** **Study 2:** Febuxostat is a non-purine analogue and is a selective inhibitor of oxidized and reduced forms of Xanthine Oxidase that significantly reduces serum uric acid levels. The present research work was conducted to evaluate the **repeated dose toxicity** of Febuxostat in Sprague Dawley rats. The animals were divided in 5 different groups each included 6 male and 6 female animals. They were administered Febuxostat at 0 (vehicle only), 2, 10, 50 and 10 (Recovery) mg/kg, orally for 28 days respectively. The animals were observed for clinical signs and growth parameters. Hematological, biochemical, urine analysis, necropsy, organ weight and Histopathological studies were conducted. **Oral administration of Febuxostat did not produce any toxic symptoms** and there was no any change in feed

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	consumption, body weight and body weight gain as compared to control group. No significant hematological alterations were noticed up to 10 mg/kg dose in both sexes. Leukocytosis with neutrophilia was noted in both sexes at 50 mg/kg dose group. There was increase in urea, creatinine and phosphorus along with decrease in calcium and sodium in the serum of male and female from dose group of 50 mg/kg. The dose dependent reduction in serum uric acid level was observed in animals of both sexes from group II, III, IV and V. Urine was yellowish and turbid in the animals of dose group 10 mg/kg and 50 mg/kg. Microscopic examination showed presence of erythrocytes and amorphous crystals in the male and female animals of dose group 50 mg/kg. The significant increase in relative weight of kidney was found in both the sexes of high dose group only. Gross pathological changes observed in the kidney of both the sexes in high dose group were paleness, flabbiness, enlargement and pinpoint whitish necrotic foci on the surface. Urinary bladder in this group showed distention with presence of yellowish urine with fine granular material. Histopathological changes were seen only in kidneys and urinary bladder of animals from group III and IV. Major Histopathological changes observed in the kidneys were hyaline deposits in kidney tubules, basophilia of tubules, thickening of glomerular basement membrane, cystic dilatation of tubules, infiltration of inflammatory cells in intertubular space, proliferation of interstitial cormective tissue, neovascularization, necrosis of tubular epithelium, presence of necrosed inflammatory cells in tubular lumen, deposition of crystals in collecting tubules and papillary duct and papillary epithelial hyperplasia. The drug Febuxostat was found effective in reducing serum uric acid levels in normal SD rats and was found nephrotoxic at dose levels of 10 and 50 mg/kg. **The NOAEL was 2 mg/kg in SD rats.** **Study 3:** A 12 month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately 4 times the MRHD on an AUC basis). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg/kg (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively). **CLINICAL STUDIES** A serum uric acid level of less than 6 mg/dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout. **Management of Hyperuricemia in Gout** The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥8 mg/dL. **Study 1 randomized patients to:** ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Clcr) ≥60 mL/min or 200 mg daily for patients with estimated Clcr ≥30 mL/min and ≤59 mL/min). The duration of

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	Study 1 was six months. **Study 2 randomized patients to:** placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤1.5 mg/dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg/dL and ≤2 mg/dL). The duration of Study 2 was six months. **Study 3, a 1 year study, randomized patients to:** ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Patients who completed Study 2 and Study 3 were eligible to enroll in a Phase 3 long-term extension study in which patients received treatment with ULORIC for over three years. In all three studies, patients received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was six months; in Study 2 and Study 3 the duration of prophylaxis was eight weeks. The efficacy of ULORIC was also evaluated in a four week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Patients who completed this study were eligible to enroll in a long-term extension study in which patients received treatment with ULORIC for up to five years.
Carcinogenicity	**Study 1:** In male mice, a tumorigenic effect was not observed up to doses of 18.75 mg/kg/day (4x human plasma exposure at 80 mg/day Febuxostat). In female rats, a tumorigenic effect was not observed up to doses of 24 mg/kg/day (20x human plasma exposure based on AUC at 80 mg/day Febuxostat). In male rats, a statistically significant increase in urinary bladder tumors (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumor type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use. **Study 2:** Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of the urinary bladder was observed at 24 mg/kg (25 times the MRHD on an AUC basis and 18.75 mg/kg (12.5 times the MRHD on an AUC basis) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder. Febuxostat showed a positive clastogenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation in vitro. Febuxostat was negative in the following Genotoxicity assays: the in vitro Ames assay, in vitro chromosomal aberration assay in human peripheral lymphocytes, the L5178Y mouse lymphoma cell line assay, the in vivo mouse micronucleus assay, and the rat unscheduled DNA synthesis assay. Fertility and reproductive performance were unaffected in male or female rats that received Febuxostat at oral doses up to 48 mg/kg/day (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).
In vivo/In vitro Genotoxicity Studies	A standard battery of test for Genotoxicity did not reveal any biologically

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	relevant genotoxic effects for Febuxostat.
Reproductive/Developmental Toxicity	**Study 1:** **There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to Febuxostat**. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects. **Study 2:** Animal Data in an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, **Febuxostat was not teratogenic** and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, Febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, Febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day). Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.
Highly Sensitizing Potential	Febuxostat does not have any sensitivity effect over skin.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Oral administration of Febuxostat did not produce any toxic symptoms
Clinical therapeutic and adverse effects	**Usual Adult Dose for Gout** **Initial dose:** 40 mg orally once a day -If serum uric acid level is greater than 6 mg/dL after 2 weeks, increase the dose to 80 mg orally once a day **Maintenance dose:** 40 to 80 mg orally once a day **Maximum dose:** 80 mg/day **The more common side effects of Febuxostat include:** • Nausea • Joint pain • Rash • Inaccurate liver function test results • Gout flare-ups

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NOAEL/LOAEL	The no observed adverse effect level (NOAEL) for 26-week rat study was considered to be 12 mg/kg/day (8x plasma exposure at 80 mg/day).

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)	2	26 weeks study in rodents
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	The no observed adverse effect level (NOAEL) for 26-week rat study was considered to be 12 mg/kg/day (8x plasma exposure at 80 mg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{12 (NOAEL) x 50}}{\text{5 x 10 x 2 x 1 x 5}}$ = 1.2 mg/day

5. REFERENCES:

- https://mri.cts-mrp.eu/human/downloads/AT_H_0939_001_PAR.
- https://krishikosh.egranth.ac.in/handle/1/5810054152.
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021856s011lbl.
- https://www.drugs.com/dosage/febuxostat.