# PERMITTED DAILY EXPOSURE FOR OCCARBAZAPINE

## 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 Oxcarbazepine 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:

Oxcarbazepine is a medication used to treat epilepsy and bipolar disorder. For epilepsy it is used for both focal seizures and generalized seizures. It has been used both alone and as add-on therapy in people with bipolar who have had no success with other treatments. It is taken by mouth.

Common side effects include nausea, vomiting, dizziness, drowsiness, double vision and trouble with walking. Serious side effects may include anaphylaxis, liver problems, pancreatitis, suicide, and an abnormal heart beat. While use during pregnancy may harm the baby, use may be less risky than having a seizure. Use is not recommended during breastfeeding. In those with an allergy to carbamazepine there is a 25% risk of problems with Oxcarbazepine. How it works is not entirely clear.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

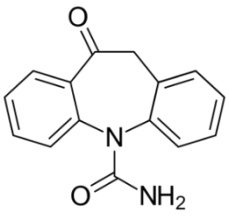
**IUPAC name:** 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine-5-carboxamide

**Chemical Abstract Services (CAS) Registry Number:** 28721-07-05

**Molecular Weight:** 252.268 g/mol $g \cdot mol^{-1}$

**Chemical Formula:** $C_{15}H_{12}N_2O_2$

**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** | Oxcarbazepine found to show anticonvulsant properties in seizure models done on animals. These compounds had protective functions whenever tonic extension seizures were induced electrically, but such protection was less apparent whenever seizures were induced chemically. There was no observable tolerance during a four weeks course of treatment with daily administration of Oxcarbazepine in electroshock test on mice and rats. Most of the antiepileptic activity can be attributed to licarbazepine. Aside from its reduction in side effects, it is presumed to have the same main mechanism as carbamazepine, sodium channel inhibition, and is generally used to treat the same conditions. |
| **Pharmacokinetics data** | Oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged Oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites. The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours, so that MHD is responsible for most antiepileptic activity.<br>**Absorption**: Based on MHD concentrations, tablets and suspension were shown to have similar bioavailability. After single-dose administration of tablets to healthy male volunteers under fasted conditions, the median t ma x was 4.5 (range 3 to 13) hours. After single-dose administration of oral suspension to healthy male volunteers under fasted conditions, the median t ma x was 6 hours. Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when is given twice a day. At steady state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day. Food has no effect on the rate and extent of absorption of Oxcarbazepine from tablets. Although not directly studied, the oral bioavailability of the suspension is unlikely to be affected under fed conditions. Therefore, tablets and suspension can be taken with or without food.<br>**Distribution:** The apparent volume of distribution of MHD is 49 L. Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein. **Metabolism and Excretion:** Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of tablets. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD). Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged Oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and Oxcarbazepine account for 13% of the dose. The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours. |

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## SUMMARY OF HAZARD IDENTIFICATION:

**Acute Toxicity**

Acute toxicity studies were performed with Oxcarbazepine (GP 47680) and its major human metabolite (GP 47779). The results indicate that GP 47680 and GP 47779 were practically nontoxic when given by single-dose administration to mice, rats, hamsters, rabbits or dogs.

| Species | Route | N/dose | Dose (mg/kg) | LD50 |
|---|---|---|---|---|
| GP 47680 (Synthesis 1) | | | | |
| Mice | Oral Gavage | 5M/5F | 100, 300, 1000, 3000, 4500 or 6000 in 2% CMC or at 5000 in acacia | in CMC: 5000 (3900-6500) In acacia: > 5000 |
| Mice | Oral Gavage | 5M/5F | 0.1, 1, 10, 100, 300, 1000, 2000, 3000 or 6000 in 0.5% CMC-Na | > 6000 |
| Rat | Oral Gavage | 5M/5F | 100, 300, 1000, 3000, 4500 or 6000 in 2% CMC | > 6000 |
| Rat | Oral Gavage | 1 to 5 M/ 1 to 5 F | 100, 300, 1000, 3000, 4500 or 6000 in 2% CMC or at 5000 in acacia | In 2% CMC: > 6000 In acacia: > 5000 |
| Rat | Oral Gavage | 5M/5F | 0.1, 1, 10, 100, 300, 1000, 3000 or 6000 in O.5% CMC-Na | > 6000 |
| Rat | Oral Gavage | 5M/5F | 0 or 1800 as a 6% suspension in syrup | > 1800 |
| Hamsters | Oral Gavage | 5M/5F | 3000 or 6000 in 0.5% CMC-Na | > 6000 |
| Rabbits | Oral Gavage | 3M/3F | 5000 in acacia | > 5000 |
| Beagle Dogs | Oral Gavage | 1F | 0, 600 or 1200 as a 6% suspension in syrup | - |
| Mice | i.p. | 5M/5F | 0.1, 1, 10, 100, 1000, 3000, 4000, 4500, 5000 or 6000 in 0.5% CMC-Na | 4310 (4070-4560) |
| Rats | i.p. | 5M/5F | 0.1, 1, 10, 100, 1000, 3000, 4000 or 6000 in 0.5% CMC-Na | 4130 (3600-4740) |
| GP 47779 (Synthesis 1) | | | | |
| Mice | Oral Gavage | 5M/5F | 10, 100, 300, 600, 1000, 2000 or 3000 in 0.7% CMC | 1240 (960-1600) |
| Rats | Oral Gavage | 5M/5F | 10, 100, 300, 600, 1000, 3000, 4500 or 6000 in 0.7% CMC | 4520 (3620-5630) |
| Neonatal rats | Oral Gavage | 10 | 10, 100, 150, 200, 250, 300, 600, 1000 or 3000 in 0.7% CMC | 205 (183-229) |
| Hamster | Oral Gavage | 5M/5F | 10, 30, 100, 300, 600, 1000, 3000 or 6000 in 0.7% CMC | > 6000 |
| Dogs | Oral Gavage | 1M/1F | 30, 100, 300 or 1000 | Doses ≥ 100 were emetic |
| Rabbits | i.v. | 2M/2F | 3, 10, 30, 60, 100, 200 or 300 in PEG 400 | 100 to 200 (M) 100 to 300 (F) |
| Dogs | i.v. | 1M/1F | 3, 10, 30, 100 or 200 in PEG 400 | > 200 |
| Mice | i.p. | 10M/10F 1 | 10, 30, 100, 150, 200, 250, 300, 350, 400, 600 or 800 in 0.7% CMC | 338 (320-358) |
| Rats | i.p. | 10M/10F 1 | 10, 100, 300, 400, 500, 600, 700, 1000, 3000 or 6000 in 0.7% CMC | 484 (448-524) |

# PERMITTED DAILY EXPOSURE FOR OCCARBAZAPINE

## SUMMARY OF HAZARD IDENTIFICATION:

**Repeated Dose Toxicity (Chronic Toxicity)**

Sub-acute and chronic toxicity studies were performed with Oxcarbazepine (GP 47680) and its major human metabolite (GP 47779). In chronic toxicity studies in rats and dogs, the only significant effects were sedation, ataxia, tremors and lack of body weight gain at higher doses. These represented exaggerated pharmacological effects and they are manifested in patients as ataxia, headache, dizziness and somnolence. Other findings were encountered in animals at high doses, but are not considered relevant for patients. The most important of these was hepatic microsomal enzyme induction and consequent hepatotoxicity. As enzyme induction is not a feature of Oxcarbazepine therapy, liver toxicity is not a relevant safety issue for patients. Evidence of nephrotoxicity was noted in the repeated dose toxicity rat studies but not in dog or mice studies. Immunostimulatory tests in mice showed that MHD (and to a lesser extent Oxcarbazepine) can induce delayed hypersensitivity. The synthesis of GP 47680 was altered during the course of development. Since the impurity profile and particle size of the material synthesized by the new method differed from those o batches prepared using the original synthesis, pivotal toxicity studies were repeated t ascertain whether these differences altered the toxic properties of the end product. The results (not presented here) indicate that material from both synthetic processes have similar toxicity profiles. In general the toxicity tests conducted with GP 47779 produced qualitatively similar alterations to those that occurred with GP 47680. Special studies employing GP 47680 (primary dermal irritation, primary ocular irritation) and GP 47779 (intravenous irritation, intraarterial in rabbit and an in vitro hemolysis test in dogs) showed no significant adverse effects.

| Species | Route | Dose (mg/kg/day) | N/Dose | Duration | Findings |
|---|---|---|---|---|---|
| GP 47680 Synthesis 1 | | | | | |
| Mice | oral, feed | 0, 600, 1800 or 6000 ppm | 5M/5F | 3 months | ≥ 600 ppm: ↑ alanine aminotransferase and aspartate aminotransferase activities (F); and hepatocellular hypertrophy and hepatocyte necrosis (M). ≥ 1800 ppm: ↑ cholesterol, total protein, and total globulin (M); ↑ absolute and relative liver weights (M,F); and hepatocellular hypertrophy and hepatocyte necrosis (F). 6000 ppm: ↑ alanine aminotransferase activity (M); ↑ cholesterol and total protein (F); ↑ absolute and relative spleen weights (F); and fatty change in the centrilobular region of the liver and nuclear inclusion bodies (M,F). Most changes dose-dependent in severity and/or incidence. Toxicological changes restricted to the liver. |
| weanling rats | oral gavage | 0, 300, 600 or 1000 in 0.5% CMC-Na | 10M/10F | 10 days | ≥ 300: Inhibition of spontaneous motility, sedation, and ataxia; and macroscopic evidence of single or multiple ulcerations/erosions of the gastric mucosa. ≥ 600: Muscular hypotonia, stiff movements, dyspnea, and piloerection; and ↓ body weight gain. 1000: ↓ blood glucose. No histopathologic organ/tissue changes were evident. With the exception of decreased body weight gains in the mid- and high-dose M, all changes were reversible. |
| Rats | Oral gavage | 0, 100, 300, 1000 or 3000 in 0.5% CMC-Na | 10M/10F | 90 days | 100 mg/kg: Asymptomatic. ≥ 300: Hair loss (F); ↑ absolute and relative liver weights (M,F); grossly enlarged livers (M,F); and microscopic evidence of slight to marked hepatocellular hypertrophy, and cytoplasmic eosinophilic droplets in occasional |

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## SUMMARY OF HAZARD IDENTIFICATION:

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| | | | | | hepatocytes (M,F). ≥ 1000: Ataxia, muscle weakness, sedation, reduction of spontaneous motility, and rough fur (M,F); and ↓ terminal body weight (M,F). 3000: Salivation (M,F); and microscopic evidence of occasional monocellular necrosis of hepatocytes (M,F). All changes reversible by the end of the follow-up period. |
| Rats | Oral Feed | 0, 100, 300 or 1000 | 10-25 M/ 10-25F | 6 months | ≥ 100 mg/kg: Fluctuations in food consumption (M,F); ↓ mean body weight (F); ↑ BUN (M,F); ↑ ALAT activity (M); ↓ alkaline phosphatase (M); ↑ absolute and relative liver weights (M,F); ↑ relative kidney weights (F); grossly enlarged livers (M); microscopic evidence of liver changes characterized by hypertrophy (F); microscopic evidence of kidney changes characterized by hyaline droplet and cast formation within dilated cortical tubules (M). ≥ 300 mg/kg: ↑ relative kidney weights (M); ↓ absolute adrenal weights (F); grossly enlarged kidneys (F); microscopic evidence of liver changes characterized by nuclear pyknosis (M, F-300 mg/kg only), and cloudy swelling and hypertrophy (M); microscopic evidence of kidney changes characterized by epithelial hyperplasia and endogenous pigment in the proximal convoluted tubules (M), and hyaline droplet and cast formation within dilated cortical tubules (F). 1000 mg/kg: ↓ mean body weight (M); ↑ absolute and relative adrenal weights (M); ↑ relative adrenal weight (recovery F); grossly enlarged livers (F); microscopic evidence of liver changes characterized by endogenous pigment in the Kupffer cells (M) and hepatocytes (F), and vacuolar degeneration (F); microscopic evidence of kidney changes characterized by glomerular fibrosis and vacuolar epithelial degeneration of cortical tubules (M), and epithelial hyperplasia and endogenous pigment in the proximal convoluted tubules (F). With the exception of increases in BUN, relative adrenal weight (females), relative liver weights and the presence of hyaline casts (both sexes), hyaline droplets within dilated tubules (males), and epithelial hyperplasia in the proximal convoluted tubules (males) at 1000 mg/kg, all changes were reversible by the end of the recovery period. |
| Dogs | Oral Gelatin Capsules | 600 | 2M/2F | 10 days | Stiff movements, exaggerated gait (steppage), and slight sedation and mydriasis; ↓ body weight and food consumption; ↑ alanine aminotransferase activity, aspartate aminotransferase activity and alkaline phosphatase; ↓ hemoglobin, erythrocytes, and slight leukocytosis; and ↑ absolute and relative liver weights. No treatment-related gross or microscopic organ/ tissue changes were evident. |
| Dogs | Oral Gelatin capsules | 0, 60, 200, 200 or 600 | 3M/3F | 3 months | ≥ 60 mg/kg: ↑ liver weights (M,F). ≥ 200 mg/kg: Microscopic evidence of an ↑ in hemosiderin in the Kupffer cells of the liver (M,F). 600 mg/kg: Various occurrences of emesis (M,F); ↑ alanine aminotransferase and aspartate aminotransferase activities (M); microscopic evidence of an ↑ in hemosiderin in the kidney (M,F). There were no treatment-related changes in any of the recovery animals. |
| Dogs | Oral | 0, 60, 200 or | 8M/8F | 6/12 | ≤ 200 mg/kg: Asymptomatic. 600→400 |

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## SUMMARY OF HAZARD IDENTIFICATION:

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| | Gelatin Capsule | 6006400* | | months | mg/kg: ↓ food consumption (F); slower body weight gain (F); and slight atrophy of thymic tissue in interim-sacrifice animals (F). |
| GP 47779 (synthesis 1) | | | | | |
| Rats | oral gavage | 0, 200, 600 or 2000 in 2% CMC | 10-15M/ 10-15F | 3 months | ≥ 200 mg/kg: ↑ mean absolute and relative liver weights; and microscopic evidence of centrilobular hepatocellular hypertrophy. ≥ 600 mg/kg: Sedation, lethargy, abnormal stance when moved, and distention of the abdomen with tenseness of the musculature; retardation in growth rates; and microscopic evidence of occasional necrotic hepatocytes. 2000 mg/kg: ↓ food consumption; ↑ alanine aminotransferase activity and slight thrombocytopenia; and microscopic evidence of excess pigment in the liver cells. All changes at least partially reversible by end of recovery period. Hepatic changes attributed to occurrence of enzyme induction. |
| Rats | Oral feed | 0, 52, 164 or 549 (M) or 0, 57, 187 or 606 (F) | 30M/30F | 6 months | ≥ 52/57 mg/kg: Dose-related ↓ in mean body weight gain and food consumption; and 8 mean thrombin time. ≥ 187 mg/kg: ↑ mean alanine aminotransferase and alkaline phosphatase (F). No treatment-related gross or microscopic organ/tissue changes All treatment-related clinical changes reversible by end of recovery |
| Dogs | Oral Capsules | 0, 60, 200 or 6006400 | 3M/3F | 3 months | 60 mg/kg: Asymptomatic. Transient muscle tremors in 1F only; depression in growth rates of 2 dogs. ≥ 200 mg/kg: Ataxia, lethargy, muscle or whole body tremors, salivation, and vomiting; ↓ food intake and/or body weight; mild to marked anemia in individual animals; microscopic evidence of extramedullary hemopoiesis of the spleen & hemosiderin in renal proximal convoluted epithelium. 600→400 mg/kg: ↑ serum Na and ↓ serum K and albumin in individual animals; ↓ absolute and relative heart weights; gross evidence of lack of body fat, distended or enlarged gallbladders, enlarged spleen, and atrophic & hemorrhagic thymus; microscopic evidence of centrilobular hepatocellular changes, marked extramedullary hemopoiesis in the spleen, thymic atrophy, moderate increases in pigment granules in the convoluted epithelium of the kidney, & ↓ spermatogenesis. All changes reversible during recovery period. |
| Dogs | Oral Capsule | 0, 30, 100 or 3006200** | 8M/8F 6 | 6-12 months | ≥ 30 mg/kg: Ataxia and tremors; and ↑ serum Na ≥ 100 mg/kg: Emesis, salivation, depression, decreased activity, opisthotonos, stiff muscles, dilated pupils, tearing, depressed righting reflex, and increased respiration; ↑ alkaline phosphatase; ↓ erythrocytic parameters; and ↑ absolute and relative liver weights. 300→200 mg/kg: ↓ locomotor activity/lethargy, recumbency/prostration, nystagmus, thinness, jerky head movements/bobbing head, instability, ptosis, relaxed nictitating membrane, exophthalmus, anorexia, and dehydration; transient, initial body weight loss, depressed body weight gain and total food consumption; and ↓ reticulocyte counts. No evident treatment-related gross or microscopic organ/ tissue changes. Majority of compound-related changes reversible by end of recovery period |
| Rats | i.v. | 0, 5, 12.5 or | 5M/5F | 14 days | 5 mg/kg: No significant findings. ≥ 12.5 |

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## SUMMARY OF HAZARD IDENTIFICATION:

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| | | | 25 in 5% glucose solution | | | mg/kg: Irregular respiration almost daily in all animals shortly after dosing |
| | Dogs | i.v. | 3 or 10 in 5% glucose solution | 3M/3F | 14 d | > 3 mg/kg: Transient clinical signs of minimal to slight emesis, diarrhea and salivation. 10 mg/kg: Histopathological findings of minimal to slight atrophy of thymus (M), likely stress-induced, secondary to the clinical signs. No mortalities and no effects on body weight or food consumption, or on ophthalmology, neurology, cardiography or clinical pathology parameters. Minimal to slight treatment-related clinical signs correlate with CNS-stimulation and not considered to be of toxicological relevance |
| | Rats | Oral gavage | 0, 50, 200, 600 or 2000 in 0.5% CMC-Na | 10-12M/ 10-12F | 13 weeks | ≥ 50 mg/kg: ↑ water consumption (M,F); echinocytosis, polyuria and proteinuria (M,F); ↑ albumin (M); ↑ bile acids, total protein, globulin and calcium (F);↓ eosinophil count (M); and ↑ mean absolute and relative liver weights (M,F). ≥ 200 mg/kg: Dry/wet perineal staining and salivation (F); ↑ total cholesterol (M,F); ↑ bile acids, total protein, calcium and inorganic phosphorus (M); ↑ total bilirubin and albumin (F); and hepatocellular hypertrophy (M,F). ≥ 600 mg/kg: Ataxia, dehydration and hypoactivity (M,F); gasping, salivation and wet perineal staining (M); inactivity and lacrimation (F); ↓ mean body weight and percent body weight gain (M); ↑ hemoglobin, MCH, MCV and gamma-GT (M); ↑ inorganic phosphorus (F); ↓ glucose and triglyceride concentrations (M,F); ↓ prothrombin time (M); and nephropathy (M). 2000 mg/kg: Mortality (2M and 1F); rales, recumbency, and stains on fur (M,F); inactivity, lacrimation and dry perineal staining (M); gasping (F);↓ mean body weight and percent body weight gain (F); ↓ mean food consumption (M,F); ↑ hematocrit and total bilirubin (M); ↑ MCV and gamma-GT (F); ↓ WBC and lymphocyte counts (M,F); and ↓ eosinophil count (F). |

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| **Carcinogenicity** | In two-year carcinogenicity studies, Oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats.<br>**In mice:** A dose-related increase in the incidence of hepatocellular adenomas was observed at Oxcarbazepine doses ≥70 mg/kg/day or approximately 0.1 times the maximum recommended human dose (MRHD) on a mg/m$^2$ basis.<br>**In rats:** The incidence of hepatocellular carcinomas was increased in females treated with Oxcarbazepine at doses ≥25 mg/kg/day (0.1 times the MRHD on a mg/m$^2$ basis) and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated with MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m$^2$ basis) and ≥250 mg/kg/day (equivalent to the MRHD on a mg/m$^2$ basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg Oxcarbazepine/kg/day and at ≥250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day. |
| **In vivo/In vitro Genotoxicity Studies** | Oxcarbazepine increased mutation frequencies in the Ames test in vitro in the absence of metabolic activation in one of five bacterial strains. Both Oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the |

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| SUMMARY OF HAZARD IDENTIFICATION: | |
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| | Chinese hamster ovary assay in vitro in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either Oxcarbazepine or MHD in V79 Chinese hamster cells in vitro. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an in vivo rat bone marrow assay. |
| **Reproductive/Developmental Toxicity** | **Study 1:** Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose (MRHD). When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the MRHD on a mg/m2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects. In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a $mg/m^2$ basis). This dose produced only minimal maternal toxicity. In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m2 basis).<br><br>**Study 2:** In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyclicity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately two times the MRHD on a mg/m2 basis).<br>**Pregnancy Category C:** Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryo lethality, growth retardation) were observed in the offspring of animals treated with either Oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose. When pregnant rats were given Oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the maximum recommended human dose [MRHD] on a $mg/m^2$ basis). Increased embryo fetal death and decreased fetal body weights were seen at the high dose. Doses ≥300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects. In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryo fetal mortality was increased at the highest dose (1.5 times the MRHD on a $mg/m^2$ basis). This dose produced only |

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| SUMMARY OF HAZARD IDENTIFICATION: | |
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| | minimal maternal toxicity. In a study in which female rats were dosed orally with Oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m$^2$ basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m$^2$ basis). There are no adequate and well-controlled clinical studies of Oxcarbazepine in pregnant women; however, Oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. **Given this fact, and the results of the animal studies described, it is likely that Oxcarbazepine is a human teratogen**. Oxcarbazepine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| **Highly Sensitizing Potential** | A very serious **allergic reaction** to this drug is rare. However, symptoms of a serious **allergic reaction**, including fever, rash, itching/swelling (especially of the face/tongue/throat/lymph nodes), joint/muscle pain, severe dizziness, trouble breathing may occur. |

| IDENTIFICATION OF CRITICAL EFFECTS: | |
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| **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** | **Therapy for Adults:**<br>Initiate dose of 600 mg/day, given twice-a-day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the maximum recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects.<br><br>**Adverse effects:** The most common include dizziness, blurred or double vision, nystagmus, ataxia, fatigue, headaches, nausea, vomiting, sleepiness, difficulty in concentration and mental sluggishness |

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| **NOAEL/LOAEL** | NOAEL value of 3 mg/kg/day is selected [Minimum daily dose (150 mg) is selected in mg/kg/day]. |

| APPLICATION OF ADJUSTMENT FACTORS: | | |
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| **F1:** Extrapolation between species | 5 | Extrapolation from Rat to Humans. |
| **F2:** Inter Individual Variability | 10 | Used for differences between individuals in the human population. |
| **F3:** Duration of Toxicity (Repeat Dose Toxicity) | 2 | 6 months duration study in rodent. |
| **F4:** Severe Toxicity (1-10) | 1 | No any toxicity 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 | |

**PERMITTED DAILY EXPOSURE FOR OCCARBAZAPINE**

| **CALCULATION** | |
|---|---|
| **PDE Calculation** | NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)<br>F1 x F2 x F3 x F4 x F5<br>= 3 (NOAEL) x 50<br>5 x 10 x 2 x 1 x 5<br>= 0.3 mg/day |

**5. REFERENCES:**


- https://en.wikipedia.org/wiki/Oxcarbazepine
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