

## Acceptable Daily Exposure (ADE) for Clozapine

CAS No. 5786-21-0

**ADE oral = 125 µg/day**

**ADE parenteral = 70 µg/day**

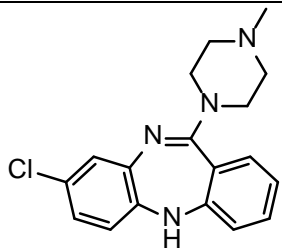
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## 1 EXECUTIVE SUMMARY

Clozapine is a tricyclic dibenzodiazepine indicated for the treatment of severely ill patients with schizophrenia. The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D<sub>2</sub>) and the serotonin type 2A (5-HT<sub>2A</sub>) receptors. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors. The most commonly reported side effects included salivary hypersecretion, somnolence, and weight gain. Pre-clinical studies with clozapine have not demonstrated carcinogenicity, mutagenicity, embryotoxicity, or teratogenicity.

## 2 DRUG PRODUCT OVERVIEW

Substance Name	Clozapine
Additional Names and Codes	Leponex, Fazaclor, Clorazil, Iprox (brand names), CAS No. 5786-21-0, HSDB 6478, CCRIS 9171, CHEBI:3766, NSC-757429
Cytotoxic*	No
Molecular Formula	C <sub>18</sub> H <sub>19</sub> ClN <sub>4</sub>
Structural Formula	 <p>The chemical structure of Clozapine consists of a central imine group (=N-) connecting two benzene rings. One benzene ring has a chlorine atom at the 4-position and a hydrogen atom on the nitrogen at the 2-position. The other benzene ring is unsubstituted. A piperazine ring is attached to the imine nitrogen at the 4-position.</p>
Molecular Weight	326.8 g/mol
Indications and target population <sup>1,2,3</sup>	Clozapine is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state.
Therapeutic Class <sup>4</sup>	Nervous system – Psycholeptics – Antipsychotics – Diazepines, oxazepines, thiazepines and oxepines / ATC code: N05AH02.
Mode of Action <sup>1,2,5</sup>	The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D <sub>2</sub> ) and the serotonin type 2A (5-HT <sub>2A</sub> ) receptors. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors.
Routes of Administration and Doses <sup>1,2,3</sup>	Clozapine is administered orally as a tablet. Usual Adult Dose for Schizophrenia Initial dose: 12.5 mg orally once or twice a day Titration and Maintenance dose: May increase total daily dose in increments of 25 mg to 50 mg per day to a target dose

	of 300 mg to 450 mg per day (administered in divided doses) by the end of week 2. Subsequent dose increases can be in increments of up to 100 mg once or twice weekly. Maximum dose: 900 mg per day
Recommended Lowest Daily Dose	12.5 mg orally daily
Contraindications <sup>1,2,3</sup>	Clozapine is contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of clozapine. Clozapine is also contraindicated in patients with myeloproliferative disorders, a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia (with the exception of granulocytopenia/ agranulocytosis from previous chemotherapy), patients with active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure, and patients unable to undergo blood tests. Clozapine should not be used simultaneously with other agents known to suppress bone marrow function.

\* A compound is considered cytotoxic if it possesses the ability to interact directly with DNA or DNA-associated macromolecules, resulting in cell death. In addition, a cytotoxic agent causes such damage in an indiscriminate manner, affecting healthy cells in addition to abnormal (e.g., tumor) cells and causing serious systemic toxicity.

### 3 CLINICAL DATA

#### 3.1 Adverse Reactions<sup>1,2,3</sup>

The most commonly reported side effects included salivary hypersecretion, somnolence, and weight gain.

##### 3.1.1 Cardiovascular

Very common (10% or more): Tachycardia (up to 25%), hypotension (up to 13%), hypertension (up to 12%). Common (1% to 10%): ECG changes, postural hypotension. Rare (0.01% to 0.1%): Arrhythmias, circulatory collapse, myocarditis, pericardial effusion, pericarditis, thromboembolism, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia. Very rare (less than 0.01%): Cardiac arrest, cardiomyopathy/clozapine-related cardiomyopathy, QT prolongation, skin reactions, Torsade de pointes. Frequency not reported: Angina pectoris/chest pain, myocardial infarction/fatal myocardial infarction, pigmentation disorder, venous thromboembolism. Postmarketing reports: Atrial fibrillation, deep vein thrombosis, mitral valve incompetence, palpitations.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion, and myocarditis have been reported. Postmarketing, very rare events of ventricular tachycardia, cardiac arrest, and QT prolongation which may be associated with Torsades de pointes have been observed, although there is no conclusive causal relationship to use of this drug.

### 3.1.2 Dermatologic

Common (1% to 10%): Rash, sweating/sweating disturbance. Frequency not reported: Leukocytoclastic vasculitis. Postmarketing reports: Erythema multiforme, photosensitivity, skin pigmentation disorder, Stevens-Johnson syndrome.

### 3.1.3 Endocrine

Postmarketing reports: Pseudopheochromocytoma.

### 3.1.4 Gastrointestinal

Very common (10% or more): Salivary hypersecretion/hypersalivation (up to 48%), salivation (up to 31%), constipation (up to 25%), nausea (up to 17%), vomiting (up to 17%), dyspepsia (up to 14%). Common (1% to 10%): Abdominal discomfort/dyspepsia/heartburn, diarrhea, dry mouth. Rare (0.01% to 0.1%): Acute pancreatitis, Dysphagia, ileus impaction, pancreatitis. Very rare (less than 0.01%): Fecal impaction/intestinal obstruction/paralytic ileus, parotid gland enlargement. Frequency not reported: Colitis, swallowing difficulty, tongue protrusion. Postmarketing reports: Intestinal infarction/ischemia/fatal intestinal infarction/ischemia, megacolon/fatal megacolon, salivary gland swelling.

### 3.1.5 Genitourinary

Common (1% to 10%): Urinary abnormalities, urinary incontinence, urinary retention. Very rare (less than 0.01%): Dysmenorrhea, ejaculation change, impotence, priapism. Postmarketing reports: Nocturnal enuresis, retrograde ejaculation.

### 3.1.6 Hematologic

Common (1% to 10%): Decreased white blood cells, eosinophilia, leukocytosis, leukopenia, neutropenia. Uncommon (0.1% to 1%): Agranulocytosis. Rare (0.01% to 0.1%): Anemia. Very rare (less than 0.01%): Thrombocythemia, thrombocytopenia. Postmarketing reports: Elevated hematocrit, elevated hemoglobin, granulocytopenia, increased erythrocyte sedimentation rate, mild leukopenia, moderate leukopenia, severe leukopenia, thrombocytosis.

During pre-marketing testing, the cumulative incidence of agranulocytosis at one year was reported to be 1.3%. Based on Clozaril National Registry (US patients) data collected up to April 1995, a hematologic risk analysis found the incidence of agranulocytosis rises steeply during the first 2 months, peaks at approximately the third month, and decreases at 6 months of therapy; after 6 months, the incidence decreases further, however, it never reaches zero. Individuals with an initial episode of moderate leukopenia (WBC of at least 2000/mm<sup>3</sup> and less than 3000/mm<sup>3</sup>) are at an increased risk of having a subsequent episode of agranulocytosis.

In the UK, agranulocytosis occurred within the first 18 weeks in approximately 70% of patients who developed the condition.

In clinical trials, eosinophil counts of greater than 700/mm<sup>3</sup> occurred in approximately 1% of patients. Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion, although it is unknown whether eosinophilia is a reliable predictor of carditis.

### 3.1.7 Hepatic

Common (1% to 10%): Elevated liver enzymes. Rare (0.01% to 0.1%): Cholestasis, cholestatic jaundice, hepatitis. Very rare (less than 0.01%): Fulminant hepatic necrosis. Postmarketing reports: Cholestatic injury, hepatic cirrhosis, hepatic fibrosis, hepatic injury, hepatic necrosis, hepatic steatosis, hepatotoxicity, jaundice, liver failure, liver transplant, mixed injury.

### 3.1.8 Hypersensitivity

Frequency not reported: Angioedema. Postmarketing reports: hypersensitivity reactions.

### 3.1.9 Metabolic

Diabetes mellitus occurred in patients without a history of hyperglycemia or diabetes mellitus.

Pooled data from 8 studies in patients with schizophrenia found the mean change in fasting blood glucose in clozapine treated patients was +11 mg/dL; pooled data from 10 studies revealed clozapine treatment was associated a mean increase of 13 mg/dl in total cholesterol; pooled data from 11 studies showed a weight gain of 7% or greater relative to baseline body weight occurred in 35% of patients with a mean weight gain of 3.7 kg.

Very common (10% or more): Increased weight/weight gain (up to 31%). Common (1% to 10%): Anorexia. Rare (0.01% to 0.1%): Aggravated diabetes, diabetes mellitus, hyperosmolar coma, impaired glucose tolerance, ketoacidosis, severe hyperglycemia. Very rare (less than 0.01%): Hypercholesterolemia, hypertriglyceridemia. Frequency not reported: Pseudopheochromocytoma. Postmarketing reports: Hyponatremia, hyperuricemia, obesity, weight loss.

### 3.1.10 Musculoskeletal

Common (1% to 10%): Rigidity. Rare (0.01% to 0.1%): Creatine phosphokinase elevation. Frequency not reported: Muscle pain, muscle spasms, muscle weakness, neck muscle spasm, systemic lupus erythematosus. Postmarketing reports: Rhabdomyolysis.

### 3.1.11 Nervous system

The cumulative incidence of seizure at 1 year is approximately 5% based on pre-marketing testing. The risk is dose-related.

Extrapyramidal symptoms that occur appear to be milder and less frequent than other antipsychotic drugs. There have been no reports of tardive dyskinesia directly attributable to clozapine; however, the syndrome has been reported in a few patients who were treated with other antipsychotics prior to receiving clozapine. A causal relationship can neither be established nor excluded.

Cholinergic syndrome occurred after abrupt withdrawal.

Very common (10% or more): Somnolence (up to 46%), drowsiness/sedation (up to 39%), dizziness (up to 27%), vertigo (up to 19%), headache (up to 10%). Common (1% to 10%): Akathisia, akinesia, convulsions/myoclonic jerks/seizures, dysarthria, extrapyramidal symptoms, hypokinesia, syncope, tremor. Uncommon (0.1% to 1%):

Neuroleptic malignant syndrome. Very rare (less than 0.01%): Tardive dyskinesia. Frequency not reported: Dystonia. Postmarketing reports: Abnormal EEG, cholinergic syndrome, clozapine-induced seizures, EEG changes, motor instability, myasthenic syndrome, myoclonus, paresthesia, pleurothotonus, possible cataplexy, post-discontinuation cholinergic rebound adverse reactions, sensory instability, status epilepticus.

#### 3.1.12 Ocular

Common (1% to 10%): Blurred vision, visual disturbances. Postmarketing reports: Narrow angle glaucoma, periorbital edema.

#### 3.1.13 Other

Very common (10% or more): Fever/hyperthermia (up to 13%). Common (1% to 10%): Benign hyperthermia, fatigue, temperature regulation disturbance. Very rare (less than 0.01%): Sudden unexplained death Postmarketing reports: Falls, polyserositis, sepsis.

#### 3.1.14 Psychiatric

Very common (10% or more): Insomnia (up to 20%). Common (1% to 10%): Agitation, confusion, disturbed sleep/nightmares, restlessness. Uncommon (0.1% to 1%): Dysphemia. Rare (0.01% to 0.1%): Delirium, dream activity intensification. Very rare (less than 0.01%): Obsessive compulsive disorder/symptoms. Frequency not reported: Neonatal drug withdrawal syndrome.

#### 3.1.15 Renal

Very rare (less than 0.01%): Acute interstitial nephritis/interstitial nephritis. Postmarketing reports: Renal failure.

#### 3.1.16 Respiratory

Aspiration of ingested food usually occurred in patients with dysphagia or in acute overdose.

Rare (0.01% to 0.1%): Aspiration of ingested food, lower respiratory tract infection/fatal lower respiratory tract infection, pneumonia, pulmonary embolism, respiratory arrest, respiratory depression, respiratory depression/arrest with/without circulatory collapse. Very rare (less than 0.01%): Allergic asthma. Frequency not reported: Difficulty breathing, nasal congestion, throat tightness. Postmarketing reports: Pleural effusion, sleep apnea/sleep apnea syndrome.

### 3.2 Side effects at overdose<sup>1</sup>

The most commonly reported signs and symptoms associated with clozapine overdose are: sedation, delirium, coma, tachycardia, hypotension, respiratory depression or failure; and hypersalivation. There are reports of aspiration pneumonia, cardiac arrhythmias, and seizure. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

### **3.3 Reproduction**<sup>1,3</sup>

US FDA pregnancy category: B.

There are no adequate or well-controlled studies of clozapine in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m<sup>2</sup> body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, clozapine should be used during pregnancy only if clearly needed.

### **3.4 Allergenicity**<sup>1,2,3</sup>

Allergic reactions to clozapine are uncommon.

## **4 CLINICAL PHARMACOKINETICS**

### **4.1 Protein Binding**<sup>1,2,5</sup>

Clozapine is approximately 97% bound to serum proteins.

### **4.2 Bioavailability**<sup>1,2,5</sup>

Clozapine is subject to first-pass metabolism, resulting in an absolute bioavailability of 50 to 60% (average 55%).

### **4.3 Elimination and Metabolism**<sup>1,2,5</sup>

Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive. The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady state with 100 mg twice daily dosing. A comparison of single-dose and multiple-dose administration of clozapine demonstrated that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, approximately dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg twice daily.

### **4.4 Excretion**<sup>1,2,5</sup>

Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated, and N-oxide derivatives are components in both urine and feces.

## 5 NON-CLINICAL TOXICOLOGICAL DATA

### 5.1 Single Dose Toxicity<sup>2</sup>

Mouse

Oral LD<sub>50</sub> – Male 210, Female 190 mg/kg

IP LD<sub>50</sub> – 90 mg/kg

IV LD<sub>50</sub> – 61 mg/kg

Rat

Oral LD<sub>50</sub> – Male 325, Female 225 mg/kg

IM LD<sub>50</sub> – Male 228, Female 198 mg/kg

IV LD<sub>50</sub> – 58 mg/kg

Guinea Pig

Oral LD<sub>50</sub> – Male 510, Female 681 mg/kg

Dog

Oral LD<sub>50</sub> – 145 mg/kg

### 5.2 Repeat-Dose Toxicity<sup>2</sup>

Long-Term Toxicity - Rats 26-Week Oral Toxicity Study in Rats: Clozapine was given to rats in a solution by gavage daily, 5 days a week, for 26 weeks. The doses used were 10, 20 and 40 mg/kg/day. Parameters examined included clinical signs, body weights, hematology, clinical chemistry, urinalysis as well as full necropsy (with organ weights) and histological examination. Ten mg/kg/day produced a slight increase in liver weights in the males. The 20 and 40 mg/kg/day doses caused sedation during the early weeks, and aggression during the later weeks of the study. Weight gain was somewhat impaired, and absolute and relative liver weights were slightly increased. The fore-stomach was slightly dilated in males.

100-Week Oral Toxicity Study in Rats: Rats were given clozapine mixed in their feed at concentrations corresponding to 15, 31 and 74 mg/kg/day for 100 weeks. A control group received unmedicated feed. The primary purpose of the study was to detect any possible carcinogenic potential of the drug in rats (see Carcinogenicity). In addition, the following parameters were studied: body weight, food intake, clinical signs, hematology, blood chemistry, urinalysis, urine chemistry, full necropsy (including organ weights) and histology of 30 organs. During the study, a dose- and time-dependent occurrence of increased lipopigment was observed in various organs. With the 31 and 74 mg/kg/day doses, increased lipopigment was seen in the thyroid, brain, kidney, liver, heart, spleen and skeletal muscle of animals dying or sacrificed after one year. At the terminal examination (100 weeks) pigment was also seen in the thyroid, heart and brain at the 15 mg/kg/day dose. The presence of increased amounts of pigment was not associated with significant adverse changes. The liver showed microscopic changes at all three dose levels, namely centro-lobular vacuolization and hepatocyte swelling, in addition to increased liver weights. The effects were dose-dependent. At the 31 mg/kg/day dose urine was reddened (probably due to a metabolite). BUN and SGPT levels were slightly increased at 26 and 100 weeks, and degenerative changes were seen in the testes and skeletal muscle. These findings were more intense at the high dose. Overall mortality was marginally increased in the treated rats, compared with the controls, but no dose-dependence was seen.



24-Month Oral Toxicity Study in Rats: Rats were given clozapine mixed in their feed at concentrations corresponding to 3, 10 and 35 mg/kg/day for 108 weeks. A control group received unmedicated feed. The purpose of the study was to detect any chronic toxic effects including carcinogenic potential of the drug in rats (see Carcinogenicity). The following parameters were studied: body weight, food intake, clinical signs, hematology, blood chemistry, full necropsy (including organ weights) and histology of 33 organs. Mortality of clozapine-treated rats was comparable to control rats at all time intervals. With the exception of lipofuscin pigmentation similar to that observed in the 100-week oral toxicity study there was no evidence that the treatments had affected the occurrence of diseases anticipated to occur spontaneously in laboratory rats.

Long-Term Toxicity - Mice 78-Week Oral Toxicity Study in Mice: Mice were given clozapine mixed in their feed for 78 weeks at an initial dose of approximately 40 mg/kg/day. From 32 weeks onwards, half of the treated mice were given a dose of approximately 75 mg/kg/day. Although the purpose of the study was primarily to detect any carcinogenic potential of the drug (see Carcinogenicity), the following parameters were also studied: body weight, food intake, hematology, blood chemistry, urinalysis, full necropsy (including organ weights) and histology of all major organs. During the early weeks of treatment up to 40% of the mice (including controls) had occasional skin lesions of unknown etiology, which were treated for short periods with antibiotic and antimycotic drugs. Clinical pathology results were unremarkable except for slightly increased serum glutamic oxaloacetic transaminase levels in treated mice at week 78. However, histology of the liver revealed no evidence of hepatotoxicity.

Long-Term Toxicity - Dogs 13-Week Oral Toxicity Study in Dogs: Clozapine was given in gelatin capsules to beagles 7 days a week for 13 weeks. Doses of 5, 10 and 20 mg/kg/day were used. Parameters studied included body weight, food intake, clinical signs, physical and neurological examinations, electrocardiography, hematology, clinical chemistry, urinalysis, as well as full necropsy (including organ weights) and histology. At all dose levels the following signs were observed (with evidence of dose-dependency): sedation, muscular relaxation, miosis, lacrimation, salivation, muscular tremors, prolapse of nictitating membranes, irritability and emesis. All signs disappeared within 12 hours after drug administration with the exception of salivation, which persisted in some instances for 24 hours. No toxicological changes were observed with the exception of some increases in liver weights in some dogs compared with the controls, but there was no evidence of dose-dependence. One female at the mid dose level died after 25 days of treatment. Necropsy revealed that death was due to acute pneumonia, and was not related to medication. No other deaths occurred at any dose level.

Oral Toxicity in Dogs Using Escalating Doses: Clozapine was given orally in gelatin capsules to beagle dogs at dose levels that increased daily, 7 days a week for 13 weeks. During the administration period the dose was gradually increased from 20 to 90 mg/kg/day. This high dosage was maintained from weeks 9 to 13. Thereafter, half of the dogs were sacrificed, while the remainder were entered into an 8-week drug-free recovery period before being sacrificed. Initially, with doses of 20 to 30 mg/kg/day, the dogs showed slight paresis, prolapse of the nictitating membrane, salivation, tremor and distinct dacryorrhea. With increasing doses these signs became progressively accentuated. In addition, miosis, unnatural posture, tachypnea and aggression

developed. In two dogs convulsions and ataxia were seen. All adverse signs disappeared within two weeks after ending drug administration. ECG tracings revealed decreased heart rate, prolonged QT intervals and twin-peaked T-waves in some leads. The ECG changes disappeared 4 weeks after the withdrawal of clozapine. All other clinical and postmortem examinations yielded changes that were probably not drug-induced, with the possible exception of increased kidney weights. Microscopic examinations were unremarkable. The final dose reached was roughly 60% of the acute LD<sub>50</sub>.

**One-year Oral Toxicity Study in Dogs:** Clozapine was given orally in gelatin capsules to beagle dogs at doses of 5, 10 and 20 mg/kg/day for 4 weeks, and thereafter at doses of 7.5, 15 and 30 mg/kg/day. The drug was administered 7 days a week. A control group received empty gelatin capsules. The parameters measured were the same as those described before. Clinical effects due to the pharmacological action of the drug (e.g., salivation, apathy, slight tremor and diarrhea) occurred at all dose levels in a dose-dependent fashion. However, no specific toxic effect or nonspecific evidence of overdosage was encountered. Minor coincidental lesions were seen in some dogs but no relationship to drug administration could be established.

**Long-Term Toxicity - Monkeys Two-year Oral Toxicity Study in Rhesus Monkeys:** Clozapine was given in gelatin capsules 7 days a week for 104 weeks. The dose levels used were 3 and 20 mg/kg/day (the high dose level was between 15 and 30 mg/kg/day during the early weeks). Parameters measured included clinical observation, body weights, hematology, blood chemistry, electrocardiography, ophthalmoscopy, as well as full necropsy with histological work-up of two monkeys per dose after 52 weeks and two further monkeys per dose after 104 weeks. Three mg/kg/day produced slight transient clinical signs (sedation and ptosis on day 1) and minor hematologic changes in the early weeks (slight falls in red and white blood cell counts without development of anemia or leukopenia). ECG tracings showed slightly prolonged QT intervals in individual monkeys at sporadic intervals, mostly in the first year. This dose is regarded as being a "no-toxic effect" level for the monkey. With 20 mg/kg/day the following clinical signs were seen: sedation, ptosis and salivation. Weight gain was impaired, and slight depressions of red and white cell counts were noted, although no cases of anemia or leukopenia occurred. The ECG changes were similar to those seen at the low dose level, although there was a decrease in the incidence of these changes during the second year. After one year, slightly increased lipopigment deposition in myocardial fibres was noted on postmortem examination. After two years there was a distinct brown discoloration of the heart and urinary bladder mucosa associated with pigment deposition. Similar pigment was also seen microscopically in the neurons of the CNS and the mucosa of the gallbladder. Splenic weights were slightly increased. However, no specific organ toxicity was seen.

### **5.3 Reproductive and Developmental Toxicity<sup>1</sup>**

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes, or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m<sup>2</sup> body surface area basis. In peri/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at

birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m<sup>2</sup> body surface area basis.

Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m<sup>2</sup> body surface area basis.

#### 5.4 Genotoxicity<sup>1</sup>

Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the *in vitro* mammalian V79 in Chinese hamster cells, the *in vitro* unscheduled DNA synthesis in rat hepatocytes or the *in vivo* micronucleus assay in mice.

#### 5.5 Carcinogenicity<sup>1</sup>

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m<sup>2</sup> body surface area basis.

### 6 DETERMINATION OF ADE

#### 6.1 Selection of Point of Departure (POD)

The point of departure dose for the ADE calculation is 12.5 mg/day orally corrected for an average bioavailability of 55% as systemic dose is important from the standpoint of potential occupational exposure.

	Value	Comments
Point of departure (POD) calculation (mg/day)	12.5	Lowest clinical dose administered orally
UF <sub>C</sub> - Composite Uncertainty Factor	100	UF <sub>C</sub> = UF <sub>L</sub> × UF <sub>H</sub> × UF <sub>A</sub> × UF <sub>S</sub> × UF <sub>D</sub>
UF <sub>L</sub> - Uncertainty factor for LOAEL to NOAEL extrapolation	10	No NOAEL identified – Severe effects at LOEL <sup>6,7</sup>
UF <sub>H</sub> - Uncertainty factor for inter-individual variability	10	Human intra-variability - Default value
UF <sub>A</sub> - Uncertainty factor for animal-to-man extrapolation	1	Human Data
UF <sub>S</sub> - Uncertainty factor for subchronic-to-chronic extrapolation	1	Sufficient long-term preclinical/clinical data
UF <sub>D</sub> - Uncertainty factor for database incompleteness	1	Complete data set – Default value
MF - Modifying factor	1	No serious alerts
α - Pharmacokinetic factor for bioavailability (BA) adjustments	1.8	Average oral bioavailability of 55%

$$\text{ADE (mg/day)} = \frac{\text{LOAEL}}{\text{UF}_c \times \text{MF} \times \alpha}$$

ADE = Acceptable Daily Exposure (or PDE - Permitted Daily exposure)

NOAEL/LOAEL = No/Lowest Observed Adverse Effect Level

BW = Body weight (50 kg)

UF<sub>c</sub> = Composite Uncertainty Factor

MF = Modifying Factor

α = Pharmacokinetic Adjustment Factor

$$\text{ADE oral} = \frac{12.5 \text{ mg/day}}{100 \times 1 \times 1} = 0.125 \text{ mg/day} = 125 \text{ } \mu\text{g/day}$$

$$\text{ADE parenteral} = \frac{12.5 \text{ mg/day}}{100 \times 1 \times 1.8} \approx 0.07 \text{ mg/day} = 70 \text{ } \mu\text{g/day}$$

## 7 REFERENCES

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