PERMITTED DAILY EXPOSURE (PDE) & OCCUPATIONAL EXPOSURE LIMIT (OEL) OF [redacted] (ORAL)

Report No: -

SAMPLE REPORT

Prepared For:

Prepared By:

Indivirtus Healthcare Services Pvt Ltd

522, Top Floor, Taj Plaza, TDI City, Sector 118, Mohali 160059 India

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ABBREVIATIONS

ATC: Anatomical Therapeutic Chemical

BV: Breathing Volume

CAS: Chemical Abstracts Serv

Cmax: Maximum Plasma Concentration

FDA: Food and Drug Administration

GLP: Good Laboratory Practice

HBEL: Health-Based Exposure Limit

IUPAC: International Union of Pure and Applied Chemistry

MTD: Maximum tolerable dose

NIOSH: National Institute for Occupational Safety and Health

NOAEL: No-Observed-Adverse-Effect Level

NOEL: No-Observed Effect Level

NTDT: Non-Transfusion-Dependent Thalassemia

OEB: Occupational Exposure Band

OEL: Occupational Exposure Limit

PDE: Permitted Daily Exposure

POD: Point of Departure

RABS: Restricted Access Barrier System

T1/2: Elimination Half-Life

Tmax: Time to Maximum Plasma Concentration

TTC: Threshold of Toxicological Concern

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1. BASIC INFORMATION

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2. HAZARDS IDENTIFIED

Toxicity	Yes	No	Unknown
Genotoxicant		✓	
Carcinogen		✓	
Reproductive/developmental toxicant		✓	
Highly Sensitizing potential			✓
Endocrine disruptor			✓
HIGHLY HAZARDOUS PRODUCT CLASSIFICATION			
Serious target organ toxicity or other significant adverse effects at low doses (Clinical dose of 10 mg/day or dosages in animal studies of ≤ 1 mg/kg/day)		✓	
Reproductive and/ or developmental effects at low dosages (clinical dose of <10 mg/day or dosage in animal studies of ≤ 1 mg/kg/day.		✓	
Compounds with a high pharmacological potency (recommended daily dose <1 mg)		✓	

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3. SUMMARY OF RISK ASSESSMENT PROCESS

HAZARD IDENTIFICATION	
Pharmacodynamics data	[redacted] is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of [redacted] are capable of binding to 1 atom of iron. [redacted] works in treating iron toxicity by binding trivalent (ferric) iron (for which it has a strong affinity), forming a stable complex which is eliminated via the kidneys.
Acute toxicity	The acute toxicity of [redacted] was assessed in mice and rats receiving oral (0-1000 mg/kg) or intravenous (0-150 and 0-75 mg/kg, respectively) single dose. The minimum lethal oral doses were 1000 and 500 mg/kg in mice or male rats and female rats, respectively. The minimum lethal intravenous doses were 150 and > 75 mg/kg in mice and rats, respectively.
Repeated dose toxicity	Repeated dose toxicity studies were conducted in mice, rats and monkeys. Kidney was identified as the main target organ of toxicity across species, showing tubular degeneration and vacuolation. Other affected organs included the liver, gall bladder, thymus, adrenal glands, heart, GI tract, and lymphoid tissues. In rats, ocular toxicity (cataracts) was also observed. Some effects persisted after recovery, and toxicity was generally dose-dependent with multi-organ involvement, particularly in high-dose or long-term studies.
Genotoxicity	[redacted] was negative in the Ames test and an *in vitro* chromosome aberration assay with human peripheral blood lymphocytes. Positive responses were observed in an *in vitro* (V79) micronucleus screening test and in a rat *in vivo* bone marrow micronucleus assay, which may have been a result of altered hematopoiesis due to iron chelation. No response was observed in another rat *in vivo* micronucleus assay (liver) with doses up to 250 mg/kg.

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Carcinogenicity	No evidence of carcinogenicity was observed in rats (104 weeks) and mice (26 weeks) treated with [redacted]
Reproductive/Developmental toxicity	Reproductive studies were conducted in rats and rabbits. In rats no effects on male and female fertility were observed at any dose level. In rabbits no embryo-fetal toxicity was observed. In pre- and post-natal development study in rats up to 90 mg/kg increase the number of still births, increase incidence of renal anomalies in F1 pups at 30 mg/kg. However, these effects were not considered as teratogenic effects as kidney toxicity were also find in neonatal rats and were considered as nephrotoxicity associated with the [redacted]
Highly sensitizing potential	No relevant pre-clinical and clinical data regarding the sensitization potential were available in the published literature.
Endocrine disruptor	No relevant pre-clinical and clinical data regarding the endocrine disruption was available in the published literature.
Immunotoxicity potential	No relevant pre-clinical and clinical data regarding the endocrine disruption was available in the published literature.

IDENTIFICATION OF CRITICAL EFFECTS	
Sensitive indicator of an adverse effect seen in non – clinical toxicity data	The major target organ of toxicity in mice, rats and marmoset were the kidney (in all species), eye, heart, gastrointestinal tract (mice and rat) and gall bladder and bile duct (monkey). Cataracts were observed in adult rats, juvenile rats and mice.
Clinical therapeutic and adverse effects	[redacted] is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. The most common adverse effects associated with the usage of [redacted] diarrhea, vomiting, nausea, abdominal pain,

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	skin rashes, and increases in serum creatinine. In [redacted]-treated patients with NTDT syndromes, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, rash and nausea.
Therapeutic Dose	**Usual dose for transfusional iron overload:** **Initial dose:** 14 mg/kg once a day **OR** 700 mg/day (based on 50 kg adult body weight). **Maximum dose:** 28 mg/kg **OR** 1400 mg/day. **Usual dose for iron overload in non-transfusion-dependent thalassemia syndromes:** **Initial dose:** 7 mg/kg once a day **OR** 350 mg/day (based on 50 kg adult body weight). **Maximum dose:** 14 mg/kg/day OR 700 mg/day **Minimum dose:** 350 mg/day; **Maximum dose:** 1400 mg/day.

Permitted daily exposure (PDE-Adult) value (Oral)	**1.33 mg/day or 1330 µg/day**
PDE_{ORAL} for Child (10 kg body weight)	**0.266 mg/day or 266 µg/day**
PDE_{ORAL} for New-born (3.5 kg body weight)	**0.0931 mg/day or 93.1 µg/day**
PDE_{ORAL} for Premature (0.5 kg body weight)	**0.0133 mg/day or 13.3 µg/day**
Occupational exposure limit (OEL) value	**0.093 mg/m^3 or 93 µg/m^3**
Occupational exposure band (OEB)	**Level 3**

Note: *Above table will have the PDE value for population who will consume the drug under scope.*

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4. OBJECTIVE AND SEARCH STRATEGY

Pharmaceutical manufacturers are required to implement robust strategies to assess and control the risk of cross-contamination when drug products are produced in shared manufacturing facilities **(1).** As part of this requirement, health-based exposure limits (HBELs) must be established for residual active substances. These limits are typically derived through scientifically justified threshold values, such as the Permitted Daily Exposure (PDE) or the Threshold of Toxicological Concern (TTC), to ensure patient safety and regulatory compliance.

The derivation of a PDE or Occupational Exposure Limit (OEL) necessitates a comprehensive evaluation of all available pharmacological, pharmacokinetic, and toxicological data from both non-clinical and clinical sources. This assessment includes formal hazard identification, review of all relevant data sets, identification of critical adverse effects, and determination of an appropriate No-Observed-Adverse-Effect Level (NOAEL) or other suitable point of departure for risk characterization.

This document provides a consolidated summary of the pharmacological, pharmacokinetic, and toxicological information available for [redacted] to support the derivation of a health-based exposure limit. Data were obtained from authoritative and publicly accessible sources, including PubChem, Drug bank, Product monograph, FDA label and Pharmacological review, EMA and some literature articles.

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5. INTRODUCTION

[redacted] is an iron chelator used to treat chronic iron overload caused by blood transfusions. Also used in patients with non-transfusion-dependent thalassemia syndromes, and in patients with elevated liver iron concentration and serum ferritin.

Pharmacotherapeutic group: Iron chelating agent

ATC code: V03AC03

IUPAC Name: [redacted]

Chemical Abstract Service (CAS) registry number: [redacted]

Chemical description and physical properties: [redacted] is a white to slightly yellow powder. It is insoluble in water with a pH of suspension of 4.1.

Molecular formula: [redacted]

Molecular weight: [redacted]

Molecular Structure:

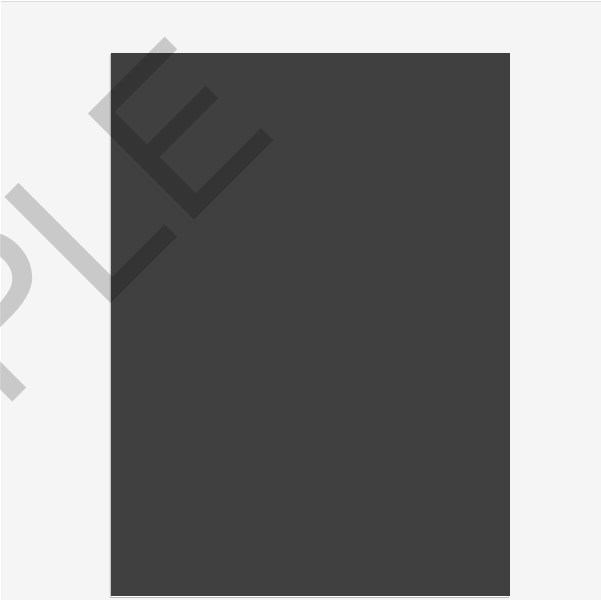


Figure 1: Structure of [redacted] **(2, 3, 4).**

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6. HAZARD IDENTIFICATION

a. Pharmacodynamics data and Mechanism of Action

[redacted] is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of [redacted] are capable of binding to 1 atom of iron. [redacted] works in treating iron toxicity by binding trivalent (ferric) iron (for which it has a strong affinity), forming a stable complex which is eliminated via the kidneys **(3, 4).**

b. Pharmacokinetics Data in Humans

Absorption: The absolute bioavailability (AUC) of [redacted] tablets for oral suspension is 70% compared to an intravenous dose.

Distribution: [redacted] is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of [redacted] confined to the blood cells was 5% in humans. The volume of distribution at steady state (Vss) of [redacted] is 14.37 ± 2.69 L in adults.

Metabolism: Hepatic. CYP450-catalyzed (oxidative) metabolism of [redacted] appears to be minor in humans (about 8%). Glucuronidation is the main metabolic pathway for [redacted] with subsequent biliary excretion.

Excretion: [redacted] and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of [redacted] and metabolites is minimal (8% of the administered dose). The mean elimination half-life ranged from 8 to 16 hours following oral administration **(3, 4).**

c. Preclinical Pharmacokinetics

Absorption: In animals (mice, rats, dogs, and marmosets), [redacted] was rapidly absorbed after oral administration**.** The absolute oral bioavailability varied across species and was approximately 58% in mice, 32% in rats, 100% in dogs, and 88% in marmosets**.** Enterohepatic recirculation was observed in bile duct–cannulated rats**,** suggesting reabsorption from the intestine.

Distribution: [redacted] and its iron complex were highly bound (>98%) to plasma proteins in all animal species studied, and the iron–complex form showed even higher binding. In blood, the compound was mainly confined to plasma, with limited uptake into blood cells in rats and mice. The steady-state volume of distribution was small to moderate in rodents and dogs (0.18–

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0.82 L/kg). Autoradiography in rats showed highest distribution in the GI tract, liver, kidney, and intestine**,** with slower elimination from skin tissue. [redacted] crossed the placenta and was excreted into milk in rats at high milk/plasma ratios.

Metabolism: [redacted] underwent extensive oxidative and conjugative metabolism in animals. In vitro studies in rat, rabbit, marmoset, and dog liver microsomes showed formation of hydroxylated metabolites (M1, M2, M4, M5). In vivo**,** oxidative metabolism was dominant in rats and marmosets**,** and glucuronidation was also a major pathway in rodents and marmosets. Overall, animals showed Phase I hydroxylation and Phase II glucuronidation and sulfation**,** indicating extensive biotransformation.

Excretion: In all animal species tested, elimination of radioactivity after oral and intravenous dosing occurred mainly via bile and feces, and was almost completely excreted within 3 days in mice and 7 days in rats and marmosets**.** Renal excretion was low, generally less than 12% of the administered dose, confirming fecal/biliary elimination as the primary route **(5).**

d. Clinical data

i. Safety and efficacy

Across the available clinical studies, orally administered [redacted] consistently lowered liver iron and serum ferritin in patients who required long-term transfusions, including those with thalassemia, sickle cell disease, and other anemias. In a head-to-head study, its ability to reduce liver iron over one year was generally similar to deferoxamine. Some longer-term observations also reported improvements in cardiac iron, although it is not yet clear how this translates into clinical benefit. However, safety studies shows side effects tended to occur more often in older patients, especially those with myelodysplastic syndromes, suggesting that treatment decisions in these individuals should balance expected benefit with the potential for harm **(3).**

ii. Special population

Pregnancy

No studies with the use of [redacted] in pregnant women to inform drug-associated risks **(3).**

Lactation

No data are available regarding the presence of [redacted] or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production **(3).**

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Pediatric Use

Among 700 patients treated with [redacted] in clinical studies, 292 were pediatric patients aged 2–<16 years, mostly with β-thalassemia. Despite younger children (2–<6 years) having about 50% lower systemic exposure than adults, the safety, efficacy, and clinical response were comparable between children and adults**,** and younger children responded similarly to older ones. Growth and development remained normal in children followed for up to 5 years. In non-transfusion-dependent thalassemia (NTDT), similar safety and efficacy were observed in pediatric patients aged 10–<16 years, with dosing recommendations the same as for adults. However, safety and effectiveness are not established in children with transfusional iron overload under 2 years of age or in NTDT patients under 10 years of age **(3).**

Geriatric Use

In clinical trials of [redacted] for transfusional iron overload, 431 elderly patients (≥65 years) were studied, most with myelodysplastic syndrome. Elderly patients showed a higher rate of adverse reactions compared to younger adults, likely due to decreased organ function and concurrent illnesses or medications. Therefore, they should be monitored closely, and dosing should be cautious, generally beginning at the lower end of the recommended range **(3).**

iii. Clinical therapeutic

Indication:

[redacted] is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older **(3).**

Dosage & administration

Therapeutic doses for [redacted] are shown in the following table **(3).**

Indications	**Usual dose**
Transfusional Iron Overload	**Initial dose:** 14 mg/kg once a day **OR** 700 mg/day (based on 50 kg adult body weight). **Maximum dose:** 28 mg/kg **OR** 1400 mg/day.
Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes	**Initial dose:** 7 mg/kg once a day **OR** 350 mg/day (based on 50 kg adult body weight). **Maximum dose:** 14 mg/kg/day OR 700 mg/day.
Minimum dose: 350 mg/day; **Maximum dose:** 1400 mg/day.	

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Adverse effects:

The most common adverse effects associated with the usage of [redacted] diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In [redacted]-treated patients with NTDT syndromes, the most frequently occurring (greater than 5%) adverse reactions are diarrhea, rash and nausea **(3).**

Warning:

WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE

[redacted] may cause serious and fatal:

- renal toxicity, including failure,
- hepatic toxicity, including failure,
- gastrointestinal haemorrhage.

[redacted] therapy requires close patient monitoring, including laboratory tests of renal and hepatic function **(3).**

e. Preclinical toxicity data

i. Acute toxicity studies

Acute toxicity studies for [redacted] are shown in the following table **(5).**

Species	**Route**	**Dose**	**Maximum non-lethal dose (mg/kg)**		**Minimum lethal dose (mg/kg)**	
			Male	**Female**	**Male**	**Female**
CD-1 mice	Oral	50, 250, 500, 1000	500	500	1000	1000
CD-1 mice	Intravenous	5, 25, 50, 150	50	50	150	150
Wistar rats	Oral	50, 250, 500, 1000	500	250	500	500
Wistar rats	Intravenous	5, 25, 50, 75	75	75	No death	No death

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ii. Repeated dose toxicity studies

Repeated dose toxicity studies for [redacted] are shown in the following table **(5, 6, 7).**

Species	Route	Dose	Duration	Key findings
Mice	Oral	134 and 268 mg/kg/day	4-weeks	**i.** Target organ toxicity appeared to be kidney (tubular degeneration at 268 mg/kg/day), thymus (atrophy at both dose levels), liver (centrilobular hypertrophy and micro vacuolation at 268 mg/kg/day) and spleen (atrophy of the spleen at 268 mg/kg/day dose level). **ii.** NOEL was not established; however, 134 mg/kg may be considered as tolerated dose.
Rats	Oral	135 and 270 mg/kg/day at a dose volume 10 ml/kg	4-consecutive weeks	**i.** One rat at 270 mg/kg/day was sacrificed on moribund condition at week 3. The cause of death was attributed to the kidney or liver toxicity. **ii.** Clinical signs at 270 mg/kg/day included sunken flanks of a slight degree (persistent as of week 2) and reddish discoloration of feces (transient) in all rats. **iii.** In addition, decrease activity, stiff gait, hunched posture, piloerection, diarrhea and muscular hypotonia of a slight to moderate degree were transiently seen in individual animals. **iv.** There were decrease in cholinesterase (high-dose) and triglyceride (dose-related). **v.** At 270 mg/kg/day, reticulocyte and thrombocyte counts were reduced in week 1.

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Species	Route	Dose	Duration	Key findings
				vi. At the end of treatment thrombocyte counts and segmented neutrophilia were slightly increase. There were no effects on organ weights. **vii.** Discoloration of kidney (pale) was noted in one animal at 270 mg/kg. **viii.** Histopathological findings included moderate tubular degeneration in the kidneys and marked thymus atrophy at 270 mg/kg. **NOAEL:** 135 mg/kg/day.
Rats	Oral	10, 30 and 100 mg/kg/day	4-consecutive weeks + 4-week recovery period	**i.** Mortality was seen at 100 mg/kg. **ii.** The target organ of toxicity was kidney (renal tubular vacuolation, tubular necrosis at 100 mg/kg), adrenal gland (vacuolation od adrenal medulla at 100 mg/kg), stomach (erosion, haemorrhage, necrosis at 100 mg/kg), heart (myocardial degeneration), large intestine (edema, erosion, haemorrhage, inflammation), small intestine (haemorrhage, epithelial hyperplasia), liver (hepatocellular hypertrophy, single cell necrosis), pancreas (atrophy of acinar cells, edema), lymph node (erythrophagocytosis, histiocytic infiltration, lymphoid depletion, lymphoid hyperplasia), spleen (atrophy) , thymus (atrophy, lymphoid depletion, haemorrhage, necrosis) and lung (haemorrhage, inflammation) at

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Species	Route	Dose	Duration	Key findings
				the dose of 100 mg/kg/day. **iii.** Following a 4-week recovery period, histopathological changes were noted in the heart and lymph node were still evident at 30 mg/kg/day (heart and lymph node) and 10 mg/kg (lymph node). **iv.** No observed adverse effects level (NOAEL) was established as 10 mg/kg/day
Rats	Oral	30, 80 and 180 mg/kg/day	26 weeks	**i.** High dose of 180 mg/kg/day was lethal and exceeded MTD (maximum tolerated dose). **ii.** At 80 mg/kg/day or higher: ophthalmologic toxicity (cataracts) and renal toxicity (increase in blood urea nitrogen and creatinine, cytoplasmic vacuolation of the cortical tubular epithelium in males) were observed. **iii.** In males, the ophthalmologic toxicity (cataracts) and increase kidney weight were observed at low dose tested (30 mg/kg/day). Therefore, MTD was identified between 30 and 80 mg/kg/day in males. In females, the dose of 30 mg/kg/day was no effect dose and ophthalmologic toxicity (cataracts) was observed at the dose of 80 mg/kg/day. The dose of 80 mg/kg/day was close to the MTD in females.
Rats	Intravenous	13.5, 27 and 54 mg/kg/day	2 weeks	**i.** The maximum tolerated dose (MTD) appeared to be 27 mg/kg/day based on 10% reduction in the body weight gain

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Species	Route	Dose	Duration	Key findings
				in males and close to 10% reduction in females relative to control. **ii.** A no observed adverse effects level (NOEL) could not be determined, as renal toxicity was observed at all tested dose levels. **iii.** The major target organ of toxicity appeared to be the kidney (tubulonephrosis, tubular basophilia/ regeneration) at all dose levels.
Marmoset monkeys	Oral	0, 100, 200 and 400 mg/kg/day	2 weeks	**i.** The target organ toxicity was appeared to kidney and gall bladder at the dose level of 200 and 400 mg/kg/day. **NOEL:** 100 mg/kg/day.
Monkey (marmosets)	Oral	400 mg/kg/day	2 weeks	**i.** No target organ of toxicity could be identified in the absence of any treatment related histopathological changes. **ii.** [redacted] at 400 mg/kg/day appeared to be well-tolerated in the iron pre-loaded marmosets under the condition of the study. **NOEL:** 400 mg/kg/day.
Monkey (marmosets)	Oral	25, 65 and 130 mg/kg/day	4 weeks + 4-week recovery period	**i.** The target organs of toxicity appeared to be kidney (vacuolar degeneration and protein casts in cortical tubules in males at 130 mg/kg/day), liver (vacuolation of intrahepatic bile duct cells in males at 130 mg/kg/day) and gall bladder (inflammation, vacuolar hyperplasia of epithelium and fibrosis of wall of gall bladder in 14 male at 130 mg/kg/day), brain (cerebral

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Species	Route	Dose	Duration	Key findings
				mineralization females at 65 and 130 mg/kg/day) and adrenal glands (adrenal cortical hemorrhage in females at 25 and 65 mg/kg/day). **ii.** Protein casts seen in a single male at 130 mg/kg/day was still evident at the end of the 4-week recovery period and a single female at 130 mg/kg/day dose level showed adrenal cortical hemorrhage at the end of the 4-week recovery period. **NOAEL:** 65 mg/kg/day in males and 130 mg/kg/day in females.
Monkeys (marmosets)	Oral	200 mg/kg/day	4 weeks	**i.** The NOEL was not established. **ii.** The target organ toxicity was appeared to be a gall bladder, liver, rectum, colon and kidney. Animals receiving iron supplemented diet tolerated treatment less well compared to the animal on normal diet.
Monkeys (marmosets) (marmosets)	Intravenous	2, 5, and 10 mg/kg/day	2 weeks	**i.** The NOAEL could not be established as histopathological changes were observed at all dose levels. **ii.** The MTD appeared to be 10 mg/kg/day in the absence of any body weight changes or mortality. The target organ toxicity was appeared to be a thyroid (focal lymphocytic infiltrations), liver (focal necrosis, bile duct hyperplasia, focal haemorrhage) and kidney (inflammation).
Monkeys (marmosets)	Oral	20, 40 and 80 mg/kg/day	39 weeks	**i.** Mortality was observed at 80 mg/kg/day.

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Species	Route	Dose	Duration	Key findings
				ii. Treatment-related findings in decedent animals on standard diet (two males and one female at 80 mg/kg/day) were observed in the gall bladder (acute inflammation and generalized degeneration and vacuolation of the hepatic bile duct) and kidneys (vacuolation and degeneration of the renal cortical tubules in all three animals and dilatation of the medullary tubules and Bowman's space in one male). **NOAEL:** 40 mg/kg/day

iii. *In-vitro/In-vivo* genotoxicity studies

In-vitro/in-vivo genotoxicity studies of [redacted] are shown in the following table **(5, 6, 7).**

Test/Assay	Cell lines/ Organism	Concentration/ Dose	Results
Ames test	*Salmonella typhimurium* strains TA1535, TA97a, TA98, TA100, TA102	Up to 5000 µg/plate with and without metabolic activation (S9)	Negative
In-vitro micronucleus test	V79 Chinese hamster cells	Up to 2500 µg/ml with S9 and up to 5000 µg/ml without S9	Positive in the presence of S9 and negative in the absence of S9. **Overall:** Positive
In-vitro micronucleus test	V79 Chinese hamster cells	Up to 600 µg/ml with S9 and up to 300 µg/ml without S9	Positive
In-vitro Chromosomal aberration test	Human peripheral blood lymphocytes	Up to 143.0 µg/mL with and without metabolic activation (S9)	Negative

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Test/Assay	Cell lines/ Organism	Concentration/ Dose	Results
In-vivo Bone marrow Micronucleus test	Rats	50, 158, 500 mg/kg/day (Orally)	Positive result at 500 mg/kg
In-vivo Bone marrow Micronucleus test	Rats	Intraperitoneal injection of iron (III)-hydroxide (40 mg/kg twice per week) for 6 weeks. Following a two-week interim phase, the animals were treated orally (two administrations with a 24-hour interval) at 300 or 500 mg/kg/day.	Negative
In-vivo Liver micronucleus test	Rats	0, 125 and 250 mg/kg/day	Negative

iv. Carcinogenicity

Carcinogenicity studies for [redacted] are shown in the following table **(5, 6, 7).**

Species	Route	Dose (mg/kg/day)	Duration	Key findings
Wister rats	Oral	25, 50 and 100 mg/kg/day of [redacted] These doses were subsequently decreased to 15, 30 and 60 mg/kg/day beginning on day 29.	104-week	No evidence of carcinogenicity was observed.
p53 Transgenic mice	Oral	Male- 0 (feed supplemented with iron), 0 (standard feed), 20, 100 and 200 mg/kg/day (feed supplemented with iron), and 30 mg/kg/day (standard feed) Female 0 (feed supplemented with iron), 0 (standard feed), 30, 100 and 300 mg/kg/day (feed supplemented with iron) and 100→60 mg/kg/day (standard feed, dose decrease effective day 50).	26-week	

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v. Reproductive and teratogenic studies

Reproductive and developmental studies of [redacted] are shown in the following table **(5, 6, 7).**

Species	Route	Dose (mg/kg/day)	Duration	Key findings
Segment I: Fertility and early embryonic development toxicity studies				
Rats	Oral	0, 7.5, 25 or 75	**Male:** 28 days prior to mating, during the mating period until terminal sacrifice **Female:** 14 days prior to mating, during the 2-weeks mating period and through gestation day 6.	**i.** No effects on sperm count, sperm motility, or fertility in males and there were no treatment-related effects noted in females at any dose level.
Segment II: Teratology (embryofoetal development) studies				
Rats	Oral	10, 30 and 100	From day 6 to 17 gestation	**i.** At 100 mg/kg/day mortality with associated gastrointestinal lesions was observed. **ii.** Clinical signs included decreases in food consumption, body weight parameters, increases in the number of fetuses with skeletal variations without an apparent indication of teratogenicity. **iii.** The maternal liver iron was depleted in a dose-dependent manner, but there were no effects on the fetal iron level. **NOEL for maternal and embryo-fetal toxicity was 30 mg/kg/day.**
Rabbits	Oral	5, 20 and 50	From gestation day 7 through 20	**i.** Drug had no effect on the reproductive parameters and no effect on the fetal external, visceral or skeletal development.

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Species	Route	Dose (mg/kg/day)	Duration	Key findings
				ii. Drug had no effect on the iron and zinc levels in the maternal liver and in the fetuses. **NOEL for maternal toxicity was 20 mg/kg/day and 50 mg/kg/day for embryo-fetal development.**
Segment III: Pre- and post-natal toxicity study				
Rats	Oral	0, 10, 30 and 90	Gestation day 6 through lactation day 20	**i.** The NOEL for F_0 maternal toxicity and fetal growth and viability was 30 mg/kg/day. **ii.** There were drug -related effects on body weight, morphological, functional, learning/ memory or fertility parameters investigated for offspring at doses ≤ 30 mg/kg/day. Thus, the NOEL for F_1 effects was > 30 mg/kg/day.

vi. Highly Sensitizing potential

No relevant preclinical and clinical data regarding the sensitization potential was available in the published literature.

vii. Endocrine disruptor

No relevant pre-clinical and clinical data regarding the endocrine disruption was available in the published literature.

viii. Immunotoxicity Potential

No relevant pre-clinical and clinical data regarding the endocrine disruption was available in the published literature.

7. IDENTIFICATION OF CRITICAL EFFECTS

Scientific evaluation of published pharmacological and toxicological data including clinical and non-clinical reports helps to identify the adverse effect of the active substances. The critical effect of the active substance is one that meets the severity and persistence criteria at the lowest intake to define the hazard associated with the intake.

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a. Most sensitive indicator of an adverse effect seen in clinical data

[redacted] is associated with a serious and fatal warning of renal failure, hepatic failure, and gastrointestinal hemorrhage.

b. Most sensitive indicator of an adverse effect seen in non-clinical toxicity data

The major target organ of toxicity in mice, rats and marmoset of monkeys were the kidney (in all species), eye, heart, gastrointestinal tract (mice and rat) and gall bladder and bile duct (marmoset). Cataracts were observed in adult rats, juvenile rats and mice.

8. APPLICATION OF ADJUSTMENT FACTORS (RATIONALE FOR THE ADJUSTMENT FACTORS)

A series of modifying or safety factors are used when NOAEL/LOAEL is based on studies of different types and duration in different species to provide a risk assessment for human exposure **(8, 9, 10).**

a. F1: Interspecies Difference

This factor takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area is calculated as $S= KM^{0.67}$ where M is the body mass and K is constant, has been taken to be 10 according to the appendices 1 of the ICH Q3D guideline. For a 50 kg person, the equation gives a surface area of $64.3dm^2$; the surface area: body weight ratio is thus 2.76. The multiples of the human surface area: body weight ration gives factors for the mouse=12, rat=5, monkey=3, rabbit=2.5, and dog=2.

b. F2: Inter-individual differences

A factor of 10 is conventionally used to allow for differences between individuals in the human population.

c. F3: Duration of exposure

A variable factor up to 10 is used for the duration of the exposure factor in the reported studies. For reproductive studies, a factor of 1 is used if the whole period of organogenesis is covered. A factor of 2 is used for a 6-month study in rodents or 3.5-year study in non-rodents. Factor 5 has been used for a 3-month study in rodents or a 2-year study in non-rodents and a factor of 10 for shorter duration studies.

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d. F4: Nature of toxicity

A variable factor is applied when the toxicity produced is irreversible in nature i.e., carcinogenicity, neurotoxicity or teratogenicity. A factor of 10 is used when oncogenic or neurotoxic responses are present. A variable factor is used for reproductive toxicity as follows. 1 for the embryo or fetal toxicity or mortality associated with maternal toxicity; 5 for the embryo or fetal toxicity or mortality without maternal toxicity; 5 for a teratogenic effect with maternal toxicity and 10 for a teratogenic effect in the absence of accompanying maternal toxicity.

e. F5: NOAEL vs LOAEL/quality of data

A variable factor of 1- 10 is applied based on selection of NOAEL/LOAEL value.

f. PK CORRECTION (α)

A variable factor is applied because PDE value derived for an active substance (contaminant) generally is based on studies applying the intended clinical route of administration, a different route of administration may be applied for the active substance or medicinal product subsequently produced in the shared facility. Changing the route of administration may change the bioavailability; hence correction factors for route-to-route extrapolation should be applied if there are clear differences in route specific bioavailability. As bioavailability may vary between species, the correction factors for route-to-route extrapolation should preferably be based on human data or in the case of veterinary medicinal products, data in the relevant target animal.

g. BV (Breathing Volume)

It is volume of air inhaled during an eight-hour work shift or when the worker exposure is measured, it is calculated what concentration it would be if the exposure was constant over 8 hours called the 8-hour Time Weighted Average, or daily exposure. A healthy adult human can inhale 10 m^3 of air during an eight-hour time per day. Thus, a factor of 10 m^3/day is used for OEL calculation.

PDE and OEL Derivation:

Pre-clinical toxicity studies were conducted in rodents and non-rodents. In rat and mice major target organ of toxicity were the kidney, gastrointestinal tract, liver, heart and lymph node. In monkeys at higher doses target organ of toxicity was found to be kidney, liver, gall bladder, bile duct and deaths were also occurred. Effects were observed in all the species at different

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dose levels. Long-term studies did not demonstrate any carcinogenic or mutagenic potential associated with deferasirox. Moreover, in reproductive toxicity studies no toxicity findings were observed. Therefore, the Permitted Daily Exposure (PDE) and Occupational exposure limit (OEL) for deferasirox was established using data from NOAEL value of 40 mg/kg/day from 39-weeks monkey study is that, monkeys are more relevant to humans as compared to other species and minimum human therapeutic dose for a conservative approach.

The PDE derived with various endpoints are shown in the following table:

Study	**Point of Departure (POD)**	**Adjustment factor**	**PDE value**
Repeated dose 39 weeks toxicity study in monkeys	**NOAEL:** 40 mg/kg/day	**Weight adjustment:** 50 kg (average adult human body weight)	= (40 x 50)/ (3 x 10 x 10 x 5 x 1) = 1.33 mg/day
		F1: 3 (Extrapolation from dogs to human)	
		F2: 10 (Default)	
		F3: 10 (39 weeks study)	
		F4: 5 (Applied for warning associated with the use of deferasirox in humans)	
		F5: 1 (Selection of NOAEL value)	
		PK correction (α): **PDE:** Not required. **OEL:** The absolute bioavailability of [redacted] is 70% **(4).** Therefore, a factor of 1.43 (Inhalational/oral bioavailability ratio) is applied for OEL calculation.	
		Accumulation factor (R): Not required.	
Minimum Human	350 mg/day	**Weight adjustment:** Not required	= (350)/ (1 x 10 x 1 x 5 x 2) = 3.5 mg/day
		F1: 1 (Selection of human dose)	
		F2: 10 (Default)	

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Study	Point of Departure (POD)	Adjustment factor	PDE value
Therapeutic Dose		**F3:** 1 (Based on long duration of use in humans)	
		F4: 5 (Applied for warning associated with the use of deferasirox in humans)	
		F5: 2 (LOAEL to NOAEL extrapolation)	
		PK correction (α): Not required.	
		Accumulation factor (R): Not required.	

Among all studies, the PDE derived from the repeated dose 39 weeks toxicity study in monkeys was the lowest and therefore considered the most adequate, appropriate, and conservative value for establishing the health-based exposure limit for [redacted]

PDE CALCULATION

The PDE calculation is generally presented in the format **(8, 9).**

PDE calculation for adult:

$$\textbf{PDE}_{\textbf{(Adult)}} = \frac{\text{NOAEL (mg/kg/day) X Weight adjustment (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$$

$$= \frac{40 \text{ x } 50}{3 \text{ x } 10 \text{ x } 10 \text{ x } 5 \text{ x } 1}$$

= 1.33 mg/day

Hence, the PDE$_{(Adult)}$ value of [redacted] is 1.33 mg/day or 1330 µg/day.

Further, PDE for children population was derived by making appropriate adjustment for body weight to already derived PDE for adult population. The standard body weight value for adults of 50 kg was replaced by lower body values (Children: 10 kg, New-born: 3.5 kg, prematurely born new-born: 0.5 kg) **(11).**

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PDE calculation for children:

$$\textbf{PDE}_{\textbf{(Children)}} = \frac{\text{Adult PDE (mg/day) x Average weight of children (kg)}}{\text{Adult Body Weight (kg)}}$$

$$= \frac{1.33 \times 10}{50}$$

= 0.266 mg/day

Hence, the $\text{PDE}_{\text{(Children)}}$ value of [redacted] is 0.266 mg/day or 266 µg/day.

PDE calculation for New-born:

$$\textbf{PDE}_{\textbf{(New-born)}} = \frac{\text{Adult PDE (mg/day) x Average weight of New-born (kg)}}{\text{Adult Body Weight (kg)}}$$

$$= \frac{1.33 \times 3.5}{50}$$

= 0.0931 mg/day

Hence, the $\text{PDE}_{\text{(New-born)}}$ value of [redacted] is 0.0931 mg/day or 93.1 µg/day.

PDE calculation for Premature:

$$\textbf{PDE}_{\textbf{(Premature)}} = \frac{\text{Adult PDE (mg/day) x Average weight of Premature (kg)}}{\text{Adult Body Weight (kg)}}$$

$$= \frac{1.33 \times 0.5}{50}$$

= 0.0133 mg/day

Hence, the $\text{PDE}_{\text{(Premature)}}$ value of [redacted] is 0.0133 mg/day or 13.3 µg/day.

OEL CALCULATION

OEL can be calculated by using the formula **(10).**

$$\text{OEL (mg/m}^3\text{)} = \frac{\text{NOAEL (mg/kg/day) X Weight adjustment (kg)}}{\text{F1 x F2 x F3 x F4 x F5 x } \alpha \text{ x BV}}$$

$$= \frac{40 \times 50}{3 \times 10 \times 10 \times 5 \times 1 \times 1.43 \times 10}$$

= 0.093 mg/m^3

Hence, the OEL value of [redacted] is 0.093 mg/m^3 or 93 µg/m^3.

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9. OEL BAND

OEL BAND CLASSIFICATION **(12, 13).**

LEVELS	JUSTIFICATION
LEVEL 1 OEB	Lowest form of containment as the chemicals do not pose any threat to the workers' safety. The only containment needed is just a local extraction and ventilation of the room. It has occupational exposure limit of ≥1000 µg/m^3.
LEVEL 2 OEB	Minimal threat to the health of the worker and therefore steps should be employed in order to reduce the amount of exposure to the worker. This means that there should be a dedicated ventilation system for the room. It has an occupational exposure limit of 100 to <1000 µg/m^3.
LEVEL 3 OEB	The material is potentially hazardous to the safety of the worker. Therefore, measures should be put in place to prevent exposure. Liner systems are used to contain discharge while glove bags and flexible isolators provide a barrier. It has an occupational exposure limit of 10 to <100 µg/m^3.
LEVEL 4 OEB	Chemicals of OEB 4 level are hazardous to the safety of the worker. Therefore, stringent measures should be put in place to prevent exposure. Physical barriers ought to be present between the worker and the chemicals and materials are handled in a dedicated enclosure using glove ports. At this level, Restricted Access Barrier Systems (RABS) are employed. It has an occupational exposure limit of 1 to < 10 µg/m^3.
LEVEL 5 OEB	Chemicals at this level are extremely hazardous to the worker. Therefore, very stringent measures must be put in place to contain any form of exposure. Physical barriers ought to be present and they should be permanent. The chemicals should definitely be in a closed and isolated compartment with access only via glove ports. Even the chamber containing the chemicals should not be handled openly. It has an occupational exposure limit of < 1 µg/m^3.
Result: [redacted] lies in 3rd level band with OEL value of 93 µg/m^3.	

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ANNEXURE I: SUMMARY OF THE EXPERT CV

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