DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-882**
SERIAL NUMBER:	**Original Submission 000: April 29, 2005** **000 BP: July 8, 2005** **000 C: July 12, 2005**
DATE RECEIVED BY CENTER:	**Original Submission 000: 05/02/05** **000 BP: July 11, 2005** **000 C: July 12, 2005**
PRODUCT:	**Exjade® (Deferasirox, ICL670) Tablets for Oral Suspension**
INTENDED CLINICAL POPULATION:	**Adult and pediatric patients aged 2 years and above**
SPONSOR:	**Novartis Pharmaceuticals Corporations**
DOCUMENTS REVIEWED:	**OOO: April 29, 2005 (Pharm/Tox)**
REVIEW DIVISION:	**Division of Gastrointestinal and Coagulation Drug Products (HFD-180)**
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Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on Approvability: From a preclinical standpoint, this NDA may be approved.

B. Recommendation for Nonclinical Studies: Sponsor's maximum limit of 5

C. Recommendations on Labeling: The sponsor may be asked to modify the proposed label of Exjade as suggested in the text of this review.

II. Summary of Nonclinical Findings:

A. Brief Overview of Nonclinical Findings: The systemic toxicity of ICL670 was adequately evaluated following oral and intravenous administration in mice, rats and marmosets monkeys. ICL670 was also tested orally in juvenile mice and rats to support its use in pediatric patients aged 2 years and above. The potential genotoxicity of ICL670 was examined in an adequate battery of genotoxicity tests. The carcinogenic potential of ICL670 has also been examined in p53 heterozygous mice and Wistar Hannover rats. In addition, ICL670 has been evaluated for fertility and reproductive performance (Segment I) in rats, teratology (Segment II) in rats and rabbits and peri- and post-natal development (Segment III) in rats. Adequate safety pharmacology studies were also conducted with ICL670.

Subacute/subchronic and chronic toxicity studies were conducted in mice (4 weeks, oral), rats (2-Week, i.v. and up to 26-week, oral) and marmoset monkeys (2-week, i.v. and up to 39 weeks oral). The target organs of toxicity appeared to vary across species. The major target organs of toxicity revealed by the repeated dose toxicity studies in mice, rats and marmoset monkeys were the kidney (in all species tested), eye (mice and rats), heart (mice and rats), gastrointestinal tract (mice and rats), and gall bladder and bile duct (marmoset). Kidney findings generally consisted of renal tubular degeneration, cytoplasmic vacuolation of cortical tubular epithelial cells and tubular necrosis across all species tested. The nephrotoxicity of ICL670 was observed at doses that were approximately 1.5-4.0 times the human exposure at 20 mg/kg/day. Cataracts were observed in adult rats (on set at Week 11 at 180 mg/kg/day, 2.5 times the human exposure and then at 30 and 80

mg/kg/day at Week 26), juvenile rats (post partum Week 3, 4 and 9 at 20 and 40→30 mg/kg/day, iron-supplemented diet) and in transgenic (p53 heterozygous) mice at Week 15 at 200 and 300 mg/kg/day in supplemented male and females, respectively. Myocardial changes (multifocal myocytolysis in the ventricle at 600 mg/kg/day in both sexes with standard diet) were observed in the 4-week mice study. In addition, myocardial changes were also observed in the 4-week study in the rat (myocardial degeneration predominantly in males at 100 mg/kg/day with standard diet). Gastrointestinal effects (gastric erosions/ulcers, inflammation) were observed in mice (at 100 and 600 mg/kg/day in non-supplemented males and females, respectively, and at 450 mg/kg/day in iron-supplemented males and females) and rats (at 100 mg/kg/day in non-supplemented animals). In addition, inflammatory and degenerative changes in the gallbladder and bile ducts were seen in some marmosets at high doses (400 mg/kg/day in 4-Week studies and at 80 mg/kg/day in 39-week study). Similar findings were also observed in intrahepatic bile ducts in transgenic mice at 100 mg/kg/day (standard diet) at Week 4 and 26. The no-adverse-effect-levels (NOAEL) in mice, rats and marmoset monkeys were considered as 100, 30 and 40 mg/kg/day, respectively. The overall mean exposures ($AUC_{0\text{-}24h}$) in mice, rats and monkeys at the above NOAELs were approximately 196, 56 and 74 µg.hr/ml, respectively, which are about 0.37, 0.10 and 0.14 times, respectively, the human exposure at the proposed dose of 20 mg/kg/day ($AUC_{0\text{-}24h}$ = 1404 µmol.hr/L at Day 12 or ≈ 524 µg.hr/ml from Study No. CICL670A0104). In addition, the NOAELs in mice, rats and marmosets were approximately 2.5, 4.1 and 3.1 times the proposed human dose of 20 mg/kg/day (740 mg/m^2) based on body surface area.

The target organs identified in neonatal/juvenile animals were consistent with those observed in adults. However, juvenile mice and rats appeared to be more sensitive to the toxicity of ICL670 when compared to adults. In addition, ICL670 has been shown to cause depression in B and T cell populations in the spleen and thymus of the juvenile mice at 35 mg/kg/day independent of the iron status.

ICL670 was not genotoxic in Ames test, chromosome aberration test with human peripheral blood lymphocytes and micronucleus test with rat liver. ICL670 was genotoxic in two micronucleus tests (*in vitro*) in V79 Chinese Hamster cells and rat micronucleus test at 500 mg/kg dose level. ICL670 was not genotoxic in micronucleus test in iron preloaded rats at 500 mg/kg/day dose. In addition, no carcinogenic potential was detected in rats treated for 104 weeks at 15, 30 and 60 mg/kg/day or transgenic mice (p53 heterozygous) treated for 26 weeks at 20, 100 and 200 mg/kg/day in males and 30, 100 and 300 mg/kg/day in females.

ICL670 at oral doses up to 75 mg/kg/day (about 0.6 times the recommended human oral dose based on body surface area) was found to have no effect on

fertility and reproductive performance of male and female rats. Reproduction studies have been performed in pregnant rats at oral doses up to 100 mg/kg/day (about 0.8 times the recommended human oral dose based on the body surface area) and in pregnant rabbits at oral doses up to 50 mg/kg/day (about 0.8 times the recommended human oral dose based on the body surface area) and have revealed no evidence of fertility or harm to the fetus due to ICL670. In pre- and post-natal developmental study in rats up to 90 mg/kg/day dose (0.7 times the recommended human oral dose based on the body surface area), ICL670 caused an increase in the number of stillbirths at 90 mg/kg/day. ICL670 also caused an increased incidence of renal anomalies (short/absent renal papilla, fluid-filled kidney) in F1 pups at 30 mg/kg/day (about 0.2 times the recommended human oral dose based on the body surface area).

ICL670 crossed placental barrier and excreted into breast milk in animals. ICL670 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, caution should be exercised when ICL670 is administered to a nursing woman.

In conclusion, the non-clinical studies conducted with ICL670 appears to adequately support the administration of ICL670 to both adult and pediatric patients (2 years and over) for the treatment of transfusional iron overload, at the intended therapeutic dosage and in accordance with the proposed product labeling.

B. Pharmacologic Activity: ICL670 is an N-substituted bis-hydroxyphenyl-triazole, a representative of a new class of tridentate iron (Fe) chelator. Two molecules of ICL670 bind to one ferric atom. It has higher affinity (pM = 22.5) for iron than L1 (pM = 19.5) and lower than that of Desferal® (pM = 26.6). In bile duct cannulated rats, it was shown to be five-fold more potent than Desferal (IBE = 3- 4% vs. 18% for ICL670) and nine-fold more potent than L1 (IBE = 2% vs. 18% for ICL670). The effective oral dose was determined to be 32 mg/kg in Tif: RAI rats. In a 12-week study in iron-overloaded rats, ICL670 reduced non-heme liver iron concentration by 53% when compared to Desferal (58%) and L1 (19%) at twice the dose of ICL670. In this study, ICL670 was found to be twice as effective as Desferal and 5-fold more effective than L1. About 40% of the ^{59}Fe-ICL670 complex was excreted in the feces within 48 hr compared to 0.5%, 3%, and 67% (urine) in control, L1, and Desferal, respectively confirming the stability of the complex *in vivo*. In the iron-overloaded marmosets, at equivalent (molar) doses, the *in vivo* iron chelating efficiency of ICL670 was found to be 29% compared to 2% and 5% for L1 and Desferal, respectively. ICL670 induced iron excretion predominantly by the fecal route and approximately 10% were excreted through the urine. ICL670 was found to be highly selective for iron and does not appear to induce the excretion of zinc and copper. Overall, *in vitro* and *in*

vivo pharmacology studies with ICL670 appear to support its intended use as indicated in the proposed label.

C. Nonclinical Safety Issues Relevant to Clinical Use: Based on non-clinical findings, patients should be closely monitored for renal function and periodic ocular testing. In addition, patients should also be monitored closely for stomach and gall bladder changes while on treatment with ICL670. ICL670 crossed placental barrier and excreted into breast milk in animals. ICL670 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In addition, caution should be exercised when ICL670 is administered to a nursing woman. Pediatric patients should be monitored for potential immunosuppression. ICL670 appeared to have the potential to cause cardiovascular effects in cardiovascular safety studies such as reduction of myocardial excitability and widening of the QRS complex and prolongation of action potential duration. The sponsor has conducted an active and placebo-controlled single dose cardiovascular safety study (CICL670A2122) in healthy volunteers at 20 (n = 46) and 40 mg/kg (n = 46), which did not show any QT prolongation at any of the tested doses. However, the patients should be monitored for any potential cardiac effects periodically.