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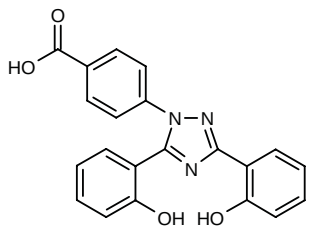
Deferasirox

Prop INN; USAN

Treatment of Iron Overload
Iron Chelator

CGP-72670
ICL-670A

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid



$C_{21}H_{15}N_3O_4$
Mol wt: 373,3665
CAS: 201530-41-8
EN: 280627

Abstract

Chronic iron overload occurs as a result of the body's inability to actively eliminate iron. The condition frequently occurs in patients with chronic anemias, such as thalassemia or sickle cell anemia, who require regular red blood cell transfusions and accumulate iron in their body tissues as a result. Without treatment, the condition can be fatal. The currently available treatment, deferoxamine, is an iron chelator which must be administered by infusion over a period of several hours, almost every day, and as a result, it has low patient acceptance. A novel tridentate, deferasirox (ICL-670A), has been developed which is orally active. Pharmacological studies in rats and marmosets have demonstrated rapid absorption and a dose-dependent effect on iron excretion, and indicated that deferasirox is a potent iron chelator. The safety, pharmacokinetics and pharmacodynamics of deferasirox have been evaluated in a number of studies in over 100 patients with β-thalassemia and transfusion-dependent chronic iron overload. The drug was well tolerated and the results of the studies indicate that deferasirox is a potent and effective oral iron chelator, a dose of 20 mg/kg preventing iron accumulation and the associated toxic effects in patients with β-thalassemia. Deferasirox has been granted orphan drug designation by the European Commission and is currently in phase III clinical development.

Synthesis

Cyclization of salicylamide (I) with salicyloyl chloride (II) by heating at 170 °C provides 2-(2-hydroxyphenyl)-benz[*e*][1,3]oxazin-4-one (III), which is finally cyclized with 4-hydrazinobenzoic acid (IV) in refluxing ethanol (1). Scheme 1.

Introduction

Patients with chronic anemias such as thalassemia or sickle cell anemia often require regular red blood cell transfusions. Repeated transfusions result in toxic, and eventually fatal, accumulation of iron, as insoluble ferritin, in various tissues of the body. This chronic iron overload occurs due to the body's inability to actively eliminate iron. Chronic iron overload is a serious condition and organ failure can occur due to the deposits of iron. When the heart or liver is affected, the condition may be life-threatening. Iron overload is treated by administration of iron chelators, which mobilize the iron deposits into soluble complexes that can be excreted from the body. The currently available first-line iron chelator, deferoxamine (Desferal®), requires intravenous or slow subcutaneous infusion over a period of 8-12 h, 5-7 times per week. This has resulted in low patient acceptance of the product. It can also cause local and systemic reactions. An orally available iron chelator, deferiprone, also has a short duration of action and may be associated with serious side effects (2-10).

Novartis therefore embarked on a major research program to identify oral iron chelators, which ultimately led to a completely new class of compounds –the bishydroxyphenyltriazoles. The best compound from this class was found to be deferasirox (ICL-670A), an orally active tridentate compound which is currently in phase III clinical development for the treatment of transfusion-dependent chronic iron overload (6).

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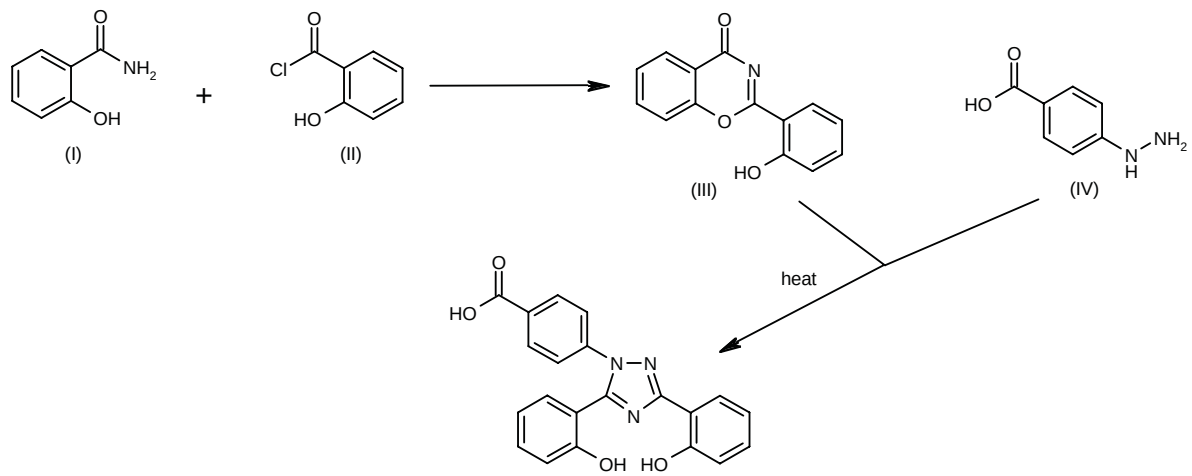
Scheme 1: Synthesis of Deferasirox



Pharmacological Actions

In a study in hypertransfused rats, selective radioiron probes were used to label hepatic parenchymal cells and reticuloendothelial cells to define the source of iron chelated *in vivo* by deferasirox. The *in vivo* effect of deferasirox was compared with deferoxamine following administration of a single 200 mg/kg dose of the drugs. The results indicated that deferasirox was 4-5 times and 2-3 times more potent than deferoxamine in promoting iron excretion from parenchymal cells and reticuloendothelial cells, respectively. The studies also demonstrated that, following treatment with deferasirox, all iron excretion, regardless of the source, was restricted to bile, whereas iron excretion following deferoxamine treatment also occurred via the kidneys. The ability of the compounds to remove iron directly from the heart was also studied in cultured iron-loaded rat heart cells. Deferoxamine was significantly better at removing heart cell radioiron, affording 73% release *versus* 46% for deferasirox, after 24-h incubation at 160 μM of either drug. The chelating efficiency of deferasirox was improved by coadministration of deferoxamine. This improvement in the chelating efficiency of deferasirox by coadministered deferoxamine was also observed *in vivo* at doses of deferaxirox up to 50 mg/kg. However, the combined effect of the drugs was not additive in the dose range of 100-200 mg/kg deferasirox, presumably because the maximum response of chelatable iron had already been reached (11, 12).

Rapid absorption of deferasirox has been demonstrated in non-iron-overloaded rats. The duration of action and area under the iron excretion time curve of deferasirox were also shown to increase with increasing dose. The efficacy of deferasirox in reducing body iron burden was compared with deferoxamine in iron-overloaded rats. Over a 12-week treatment period, deferasirox at a dose of 56 mg/kg/day orally resulted in a continuous decrease in liver iron. At the end of the treatment period, non-heme liver iron concentrations were reduced by 60% compared to untreated, iron-overloaded control rats and deferasirox was twice as effective as deferoxamine (s.c.) in this respect (13).

Rodent models, however, differ substantially from primates, including man, in their metabolism of iron, and compounds active as chelators in rodents may therefore not necessarily be active in man. For this reason, a primate model was developed. The marmoset is small and easily handled and requires similar amounts of test compounds to rats. Pharmacological actions of deferasirox have been evaluated in iron-overloaded marmosets. The animals were given intraperitoneal injections of iron(III) hydroxide and then kept in metabolic cages while iron balance studies were performed over a period of 2 days. Induction of iron excretion by single doses of deferasirox in iron-overloaded marmosets was also dose-dependent, with excretion predominantly by the fecal route. The potent iron-chelating properties of deferasirox were confirmed in the marmoset model. In these preclinical studies, deferasirox had no clinically relevant effects in iron-overloaded animals on the central nervous, respiratory or cardiovascular systems, nor on the kidney (13-15).

In vitro studies have also indicated that deferasirox may have potential as an antimalarial agent by inhibiting parasite growth by depriving critical targets within the parasite of iron (16).

Pharmacokinetics and Metabolism

A high-performance liquid chromatographic method for the determination of deferasirox and its iron complex in plasma has been developed (17).

Single- and multiple-dose pharmacokinetics of orally administered deferasirox were studied in rats and marmosets. It was rapidly and well absorbed following administration of single doses of 10 and 25 mg/kg of [^{14}C]-labeled drug in rats and marmosets, respectively. Following multiple doses in the marmoset model over 4 weeks, systemic exposure was proportional to greater than proportional, indicating saturation of the elimination process. Accumulation in plasma was marginal up to doses of 130 mg/kg (13).

In a study assessing the pharmacokinetics, metabolism and elimination of deferasirox, 5 patients with β-thalassemia were switched from deferoxamine therapy to deferasirox at a dose of 1000 mg (approximately 20 mg/kg) daily for 6 days. On day 7, patients received a single dose of [^{14}C]-labeled deferasirox, then continued with once-daily oral administration for a further 7 days. The elimination half-life of deferasirox was 11 h, lower than that observed for corresponding dose levels in a previous study. However, this was probably due to the small number of patients and substantial interpatient variability in AUC and C_{max}. The predominant route of excretion of radioactivity was via the feces (83%). Glucuronidation was assumed to be the main metabolic pathway, and hepatobiliary anion transport the final elimination process for deferasirox, its iron complex and their metabolites. The authors concluded that the potential for drug interactions via cytochrome P-450 enzymes was low (18).

Clinical Studies

The pharmacokinetics and preliminary pharmacodynamic effects of deferasirox were investigated in a randomized, double-blind, placebo-controlled study in patients with transfusion-dependent β-thalassemia. In this first-in-man study, 24 patients who had previously been treated with deferoxamine were allocated to 1 of 3 study groups and received 2 single ascending oral doses of deferasirox at least 7 weeks apart. The doses administered ranged from 2.5 to 80 mg/kg. No serious adverse events were reported. The plasma half-life of deferasirox was 11-19 h and the area under the plasma concentration curve ($AUC_{0\text{-}24\ h}$) and peak plasma concentration (C_{max}) increased almost proportionally with increasing dose. Chelation of the ligand deferasirox to iron in plasma was observed in all but 3 patients who received the lowest dose of the drug. At the lower doses, the excretion of deferasirox and its iron complex was almost exclusively in the feces. However, at doses of 40 and 80 mg/kg, there was a trend towards increased urinary excretion when $AUC_{0\text{-}24\ h}$ exceeded specific threshold values. The observed elimination half-life of deferasirox and its iron complex supported once-daily oral administration of the drug, and the results of the study indicated that deferasirox was an effective iron chelator for the treatment of chronic iron overload (19, 20). The results of this study and those that follow are summarized in Table I.

The short-term efficacy, pharmacokinetic and pharmacodynamic relationships and safety of deferasirox were studied in 24 patients with β-thalassemia and transfusional iron overload. In this randomized, double-blind, placebo-controlled, dose-escalation trial, patients were admitted to a metabolic unit and consumed a defined amount of iron. Patients received deferasirox 10, 20 or 40 mg/kg daily for 12 days. The results indicated that net iron excretion was linearly related to dose, and 5 of 6 patients in the 20 mg/kg cohort achieved levels that would prevent net iron accumulation in most patients transfused with a standard regimen of 12-15 ml packed red blood cells/kg/month. The treatment also resulted in a sustained increase in urinary iron-binding capacity (UIBC). The mean elimination half-life of deferasirox in plasma was 12-16 h and steady state was reached after 3 days of treatment. The AUC for plasma concentrations increased proportionally with dose at steady state. The only drug-related or possibly drug-related adverse events were maculopapular rash and gastrointestinal disturbances (nausea, diarrhea, abdominal pain), and no clinically relevant changes in laboratory parameters or other tests were reported. The results of the study indicated that deferasirox was an effective oral chelator and that a once-daily oral dose of 20 mg/kg would prevent iron accumulation and the associated toxic effects in patients with β-thalassemia (21-23).

An open-label, multicenter, randomized phase II study was performed in 71 patients with β-thalassemia and transfusional iron overload. Patients received deferasirox doses of 10 or 20 mg/kg/day p.o. or deferoxamine 40 mg/kg/day s.c. 5 times per week. Following long-term treatment, liver iron concentrations were assessed in 46 patients treated for 18 months. The mean liver iron concentrations decreased from baseline by 1.2 and 1.3 mg iron/g dry weight liver in patients receiving 20 mg/kg deferasirox and 40 mg/kg deferoxamine, respectively. With reference to individual changes from baseline hepatic iron burden, 60% and 75% of patients receiving 20 mg/kg deferasirox and 40 mg/kg deferoxamine, respectively, were classified as treatment successes. Pharmacokinetic and pharmacodynamic assessments up to 12 months indicated that the mean exposure (AUC) to deferasirox and its iron complex was dose-related and that liver iron concentrations were also related to drug exposure. No drug accumulation was observed at steady state following repeated daily dosing throughout the period of study. The decreases in liver iron concentrations observed in this study after 6 and 18 months' treatment with deferasirox were similar to those achieved following treatment with standard doses of deferoxamine. Skin rashes which gradually disappeared during continued treatment were seen in 2 patients on deferasirox and transient mild proteinuria occurred in all dose groups (24-27).

Phase III clinical trials are ongoing to further evaluate the safety and efficacy of deferasirox in patients with transfusional iron overload. Orphan drug designation has been granted by the European Commission.

Table I: Clinical studies of deferasirox in patients with thalassemia (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Randomized, double-blind	Deferasirox, 2.5 mg/kg → 20 mg/kg (n=8) Deferasirox, 5 mg/kg → 40 mg/kg (n=8) Deferasirox, 10 mg/kg → 80 mg/kg (n=8) Placebo	24	Deferasirox was well tolerated at single doses of up to 80 mg/kg in patients with β-thalassemia major, with only mild to moderate adverse events reported	19, 20
Randomized, double-blind, multicenter	Deferasirox, 10 mg/kg po od x 12 d (n=5) Deferasirox, 20 mg/kg po od x 12 d (n=6) Deferasirox, 40 mg/kg po od x 12 d (n=7) Placebo (n=6)	24	Deferasirox increased iron excretion and improved iron balance in patients with β-thalassemia and iron overload. Most adverse events were mild or moderate, and only 3 patients withdrew from the study due to serious adverse events related to deferasirox. A daily dose of 20 mg/kg was considered to be optimal for the treatment of β-thalassemia	21, 23
Randomized, double-blind	Deferasirox, 10 mg/kg od x 12 d (n=5) Deferasirox, 20 mg/kg od x 12 d (n=5) Deferasirox (dose dependent on the results from the other two cohorts) od x 12 d (n=5) Placebo (n=6)	21	Deferasirox was effective in achieving a substantial net negative iron balance in patients with β-thalassemia major	22
Randomized, open, multicenter	Deferasirox, 10 mg/kg sc od 5x/wk x 13.9-21.6 mo (n=15) Deferasirox, 20 mg/kg sc od 5x/wk x 13.9-21.6 mo (n=15) Deferoxamine, 40 mg/kg sc od 5x/wk x 13.9-21.6 mo (n=16)	71	Deferasirox 20 mg/kg/d was well tolerated and was as effective as deferoxamine and better than deferasirox 10 mg/kg/d in reducing the liver iron content of β-thalassemia patients with transfusional iron overload	24
Randomized, double-blind	Deferasirox, 10 mg/kg po od x 6 mo (n=22) Deferasirox, 20 mg/kg po od x 6 mo (n=21) Deferoxamine, 40 mg/kg sc od 5x/wk x 6 mo (n=20)	71	Deferasirox was well tolerated and as effective as deferoxamine in decreasing liver iron content in thalassemia patients with transfusional iron overload, with no major safety concerns	25, 26

Source

Novartis Pharma AG (CH).

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