

**MEDIA RELEASE • MEDIA RELEASE • MEDIA RELEASE****Abstracts #3873, 3875, 633****Exjade® benefits chronically transfused patients by significantly reducing toxic iron that can damage key organs, according to landmark trial**

- *First prospective, multicenter study to show Exjade removes iron from the heart in beta-thalassemia patients with mild to severe cardiac iron overload*
- *In a subgroup analysis of 341 patients with myelodysplastic syndromes (MDS), Exjade significantly reduced levels of toxic iron*
- *These results are part of the largest prospective trial in iron chelation, which includes more than 1,700 patients with various transfusion-dependent anemias*

**East Hanover, NJ, December 8, 2008** – New data from the largest prospective trial in iron chelation demonstrate the efficacy and safety of Exjade® (deferasirox) in treating chronic transfusional iron overload, a potentially life-threatening condition for patients who have had multiple blood transfusions to treat underlying anemias, including beta-thalassemia and myelodysplastic syndromes (MDS).

Data from this landmark trial, known as EPIC, were presented today at the 50th American Society of Hematology (ASH) Annual Meeting and Exposition in San Francisco, California.

The EPIC cardiac substudy showed that Exjade removed iron from the heart in beta-thalassemia patients, based on a statistically significant improvement in T2\* magnetic resonance imaging, a validated technique to assess cardiac iron content (P<0.0001). The one-year substudy included 114 beta-thalassemia patients with cardiac iron overload, the leading cause of death in these patients.

“These data clearly demonstrate that deferasirox significantly reduces cardiac iron in beta-thalassemia patients with iron overload, which is a critical goal of treatment for these patients,” said Dudley Pennell, MD, Professor of Cardiology, Royal Brompton and Harefield NHS Trust and Imperial College, London. “Cardiac complications caused by the buildup of toxic iron in the heart can be life-threatening for people living with thalassemia.”

A pre-planned analysis of 341 MDS patients enrolled in the study showed that Exjade significantly reduced levels of serum ferritin (SF), a key measure of iron in the body, by 253.0 ng/mL from baseline (P=0.0019). Of the 171 MDS patients whose SF was measured at one year, the decrease from baseline was 606 ng/mL.

"Many MDS patients receive regular blood transfusions as part of their ongoing treatment, which puts them at risk for iron overload," said Norbert Gattermann, MD, PhD, Hematology, Oncology and Clinical Immunology, Heinrich Heine University Medical Center, Dusseldorf, Germany. "This study, which includes the largest number of MDS patients of any iron chelation study, shows deferasirox can effectively reduce iron burden and is generally well tolerated when used appropriately to treat these patients."

Iron toxicity can lead to permanent damage of the liver, heart and endocrine glands, leading to an increased risk of serious health problems and early death. Previous studies of transfusion-dependent MDS patients have found that increased levels of SF are associated with shortened overall survival.

#### **About the EPIC trial**

The EPIC trial was a one-year, open-label, prospective, multicenter trial. EPIC studied the efficacy and safety of a fixed starting dose of Exjade based on transfusional iron intake, with subsequent dose titration at 3-monthly intervals based on serum ferritin (SF) trends. With 1,744 patients, this trial is the largest ever conducted for an iron chelator and included the largest cohorts of underlying anemias in a single trial, including patients with beta-thalassemia, MDS and aplastic anemia. Twelve abstracts from EPIC are being presented at ASH.

#### **Study details**

The EPIC cardiac substudy evaluated the cardiac efficacy of Exjade in 114 beta-thalassemia patients with myocardial siderosis ( $T2^* < 20$  ms). Baseline myocardial  $T2^*$  was  $< 10$  milliseconds (ms) in 47 (41%) patients (considered severe cardiac iron overload) and 10-20 ms in 67 (59%) patients (considered mild to moderate). Mean baseline liver iron concentration (LIC) was  $28.2 \pm 10.0$  mg Fe/g dry weight (dw), median SF was 5235 ng/mL, and the mean amount of transfused blood in the year prior to study entry was 185 mL/kg.

Patients experienced a statistically significant increase in myocardial  $T2^*$  indicating a decrease in myocardial iron content. Based on a geometric mean  $\pm$  coefficient of variation, change from baseline ( $11.2$  ms  $\pm 40.5\%$ ) to  $12.9$  ms  $\pm 49.5\%$  represents an increase by a factor of 1.16 from baseline ( $P < 0.0001$ ). Overall, 69.5% of patients taking Exjade had an improvement in  $T2^*$  ( $> 4\%$  increase); there was no change in 14.3%; and worsening ( $> 4\%$  decrease) in 16.2% of patients. Left ventricular ejection fraction remained stable throughout the study. Additionally, LIC and SF levels (both indicators of total body iron) were significantly reduced from baseline by  $-6.6 \pm 9.9$  mg Fe/g dw and  $-1257$  ng/mL, respectively ( $P < 0.0001$ ). Four patients discontinued treatment due to adverse events. Most investigator-assessed drug-related adverse events were mild to moderate in severity; rash was the most common (13.2%). There is an ongoing one-year extension of this substudy.

The pre-planned subgroup analysis of the EPIC study included 341 patients with transfusion-dependent MDS and SF levels  $\geq 1000$  ng/mL, or SF  $< 1000$  ng/mL, but with a history of multiple transfusions ( $> 20$  transfusions or 100 mL/kg of red blood cells) and an R2 MRI-confirmed LIC  $> 2$  mg Fe/g dw. Overall, mean actual

dose of Exjade over one year of treatment was  $19.2 \pm 5.4$  mg/kg/day. Based on the last observation carried forward statistical method, at one year, there was a significant reduction in median SF from baseline ( $-253.0$  ng/mL;  $P=0.0019$ ,  $n=341$ ). Of the 171 MDS patients whose SF was measured at one year, the decrease from baseline was  $606$  ng/mL. Overall, 48.7% of pts ( $n=166$ ) discontinued therapy. Most common investigator-assessed drug-related adverse events were mild to moderate in severity and included diarrhea ( $n=110$ , 32%), nausea ( $n=45$ , 13%), vomiting ( $n=26$ , 8%), abdominal pain ( $n=26$ , 8%), upper abdominal pain ( $n=25$ , 7%), rash ( $n=23$ , 7%) and constipation ( $n=21$ , 6%).

### **About Exjade**

EXJADE is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. Further studies are being performed to determine the long-term benefits and risks of EXJADE.

EXJADE is contraindicated in patients with hypersensitivity to deferasirox or to any other component of EXJADE.

Cases of acute renal failure, some with a fatal outcome, have been reported following the postmarketing use of EXJADE. Most of the fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematologic disorders. There have also been reports of renal tubulopathy in patients treated with Exjade. Give particular attention to monitoring serum creatinine in patients who: are at increased risk of complications, have pre-existing renal conditions, are elderly, have comorbid conditions, or are receiving medicinal products that depress renal function.

Assess serum creatinine in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Monitor serum creatinine monthly thereafter. In patients with additional renal risk factors (those who are at increased risk of complications, have pre-existing renal conditions, are elderly, have comorbid conditions, or are receiving medicinal products that depress renal function), monitor serum creatinine weekly during the first month after initiation or modification of therapy and monthly thereafter. Nonprogressive increases in serum creatinine have been noted in 38% of EXJADE-treated patients, compared to 14% of deferoxamine-treated patients in Study 1 and 36% vs 22%, respectively in Study 3, and appear to be dose related. These increases were within the normal range in 94% of patients. EXJADE dosages were adjusted when serum creatinine elevations were detected during the study.

Consider dose reduction, interruption, or discontinuation for elevations in serum creatinine. For adult patients, reduce daily dose of Exjade by 10 mg/kg if rise in serum creatinine to  $> 33\%$  above average of the pretreatment measurements is seen at 2 consecutive visits, and cannot be attributed to other causes. For pediatric patients, reduce dose by 10 mg/kg if serum creatinine levels rise above age-appropriate upper limit of normal at 2 consecutive visits. If there is a progressive increase in serum creatinine beyond the age-appropriate upper limit of normal, interrupt EXJADE use. Once the creatinine has

returned to within the normal range, therapy with EXJADE may be reinitiated at a lower dose followed by gradual dose escalation, if the clinical benefit is expected to outweigh potential risks.

Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of EXJADE-treated patients, compared to 7.2% of deferoxamine-treated patients in Study 1, and monthly monitoring is recommended.

There have been postmarketing reports of cytopenias (including agranulocytosis, neutropenia and thrombocytopenia) in patients treated with EXJADE. Some of these patients died. The relationship of these episodes to treatment with EXJADE is uncertain. Most of these patients had pre-existing hematologic disorders that are frequently associated with bone marrow failure. In line with standard clinical management, monitor blood counts regularly. Consider interrupting treatment with Exjade in patients who develop unexplained cytopenia. Reintroduction of therapy with EXJADE may be considered once the cause of the cytopenia has been elucidated.

There have been postmarketing reports of hepatic failure, some with a fatal outcome, in patients treated with EXJADE. Most of these events occurred in patients greater than 55 years of age. Most reports of hepatic failure involved patients with significant comorbidities, including liver cirrhosis and multi-organ failure. Monitor liver function tests monthly during Exjade treatment and consider dose modifications or interruption for severe or persistent elevations. In Study 1, seventeen (5.7%) patients treated with EXJADE developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits versus five (1.7%) patients treated with deferoxamine.

Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving EXJADE, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, discontinue EXJADE and institute appropriate medical intervention.

Skin rashes may occur during treatment with EXJADE. For rashes of mild to moderate severity, EXJADE may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, Exjade may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.

Auditory (high-frequency hearing loss, decreased hearing) and ocular (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) disturbances have been reported with EXJADE therapy in less than 1% of patients in clinical trials. Auditory and ophthalmic testing (including slit lamp examinations and dilated funduscopy) are recommended before the start of EXJADE treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, consider dose reduction or interruption.

Gastrointestinal (GI) irritation may occur during Exjade treatment. Upper GI ulceration and hemorrhage have been reported

in patients, including children and adolescents, receiving Exjade. Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. Use caution when administering Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants.

The most frequently occurring adverse reactions with a suspected relationship to EXJADE were diarrhea, vomiting, nausea, abdominal pain, skin rash, and increases in serum creatinine. Maintenance of adequate hydration for patients experiencing diarrhea or vomiting is recommended. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related. These commonly reported adverse events were predominantly mild to moderate in severity with serious adverse events reported in 9.1% of patients in the EXJADE arm and 8.6% of patients in the deferoxamine arm.

For full prescribing information, please visit [www.us.exjade.com](http://www.us.exjade.com)

#### **Disclaimer**

The foregoing release contains forward-looking statements that can be identified by terminology such as "potentially," "can," "risk," "will," "may," or similar expressions, or by express or implied discussions regarding potential new indications or labeling for Exjade or regarding potential future revenues from Exjade. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Exjade to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Exjade will be approved for any additional indications or labeling in any market. Nor can there be any guarantee that Exjade will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Exjade could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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**Novartis Media Relations****Denise Brashear**

Novartis Division Communications  
862 778 7336 (direct)  
917 453 2665 (mobile)  
[denise.brashear@novartis.com](mailto:denise.brashear@novartis.com)

e-mail: [media.relations@novartis.com](mailto:media.relations@novartis.com)

**Novartis Investor Relations****North America:**

Richard Jarvis	+1 212 830 2433
Jill Pozarek	+1 212 830 2445
Edwin Valeriano	+1 212 830 2456

e-mail:  
[investor.relations@novartis.com](mailto:investor.relations@novartis.com)