

# Novartis drug Zortress® is first in over a decade approved by FDA to prevent organ rejection in adult liver transplant patients

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- - Zortress is the first mTOR inhibitor approved to prevent organ rejection in adult liver transplant patients in the US, where it is already approved for kidney transplantation
- - Approval based on positive outcomes from largest liver transplant study ever, comparing Zortress plus reduced-exposure tacrolimus to standard tacrolimus<sup>1</sup>
- - Under trade name Certican®, the drug was approved by European Health Authorities for use in adult liver transplant patients in the fourth quarter of 2012

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EAST HANOVER, N.J., Feb. 15, 2013 /PRNewswire/ -- Novartis announced today that the US Food and Drug Administration (FDA) has approved Zortress® (everolimus) for the prophylaxis of organ rejection in adult patients receiving a liver transplant. Zortress is the first mammalian target of rapamycin (mTOR) inhibitor approved for use following liver transplantation. It is also the first immunosuppressant approved by the FDA in over a decade for use following liver transplantation.<sup>1</sup>

"Novartis has been a leading innovator in the transplant field for 30 years, and this FDA approval for liver transplantation marks an important milestone for patients and their transplant physicians in the US," said David Epstein, Division Head of Novartis Pharmaceuticals. "This second indication for Zortress in just three years in the US follows the recent European approval, further underscoring Novartis' continued commitment to bringing much needed treatment options to the transplant community worldwide."

The approval was based on the largest liver transplant study to date, which showed that Zortress plus reduced tacrolimus led to comparable efficacy and 10mL/min higher renal function as measured by estimated glomerular filtration rate (eGFR) for Zortress compared to standard tacrolimus at 12 months.<sup>1</sup>

"While prevention of acute organ rejection is a key priority for physicians following liver transplantation, managing other health risks, including impaired renal function associated with calcineurin inhibitor treatment, is also critical," said John Fung, M.D., Ph.D., Director, Transplantation Center, Cleveland Clinic Foundation, Cleveland, OH. "With the approval of Zortress, the first mTOR inhibitor approved for liver transplant patients, we have a new treatment option that has the potential to address the unmet medical need for maintaining renal function without compromising acute rejection rates – and that's important for patients and physicians."

A large independent registry study of nearly 70,000 patients who received a non-renal solid organ transplant between 1990 and 2000 showed that the incidence of chronic renal failure was greater in liver transplant recipients than in recipients of all other solid organ transplants, except intestinal transplants.<sup>2</sup> Calcineurin inhibitors (CNIs), such as tacrolimus, are part of the standard-of-care treatment regimen for

immunosuppression in liver transplantation, but they can contribute to adverse reactions, including impaired renal function.<sup>3,4</sup> Zortress works by binding to a protein called mTOR, and acts synergistically with CNIs, offering an opportunity to lower CNI exposure.<sup>1,5</sup>

European Health Authorities approved Certican<sup>®</sup> (everolimus) for the prophylaxis of organ rejection in adult patients receiving a liver transplant in the fourth quarter of 2012. In most EU member countries, Certican is also approved in kidney and heart transplantation. In the US, Zortress is already approved for use in adult kidney transplant patients.<sup>1</sup>

#### Pivotal Study Details: Zortress Plus Reduced-Exposure Tacrolimus

The US approval was based on 12-month results from a Phase III, multicenter, open-label, randomized, controlled study conducted in 719 liver transplant patients starting 30 days post-transplant. In liver transplantation, Zortress is to be administered no earlier than 30 days post-transplant concurrently in combination with reduced doses of tacrolimus and with corticosteroids. Therapeutic drug monitoring is recommended. In the study, during the first 30 days after transplant and prior to randomization, patients received tacrolimus and corticosteroids, with or without mycophenolate mofetil. No induction antibody was administered.<sup>1</sup>

Thirty days following liver transplantation, patients were randomized to one of three groups: Zortress (C<sub>0</sub> 3-8ng/mL) plus reduced-exposure tacrolimus (C<sub>0</sub> 3-5ng/mL) (n=245), Zortress (C<sub>0</sub> 6-10ng/mL) followed by tacrolimus withdrawal at four months (n=231) or standard-exposure tacrolimus (C<sub>0</sub> 6-10ng/mL) only (control, n=243). All three study arms included twice-daily treatment. Additionally, all arms included corticosteroids for at least six months post-transplant. Enrollment into the tacrolimus withdrawal arm was prematurely halted due to a higher incidence of acute rejection episodes and adverse reactions leading to treatment discontinuation, clustered around the time of tacrolimus elimination at four months post randomization. Therefore, a treatment regimen of Zortress with tacrolimus elimination is not recommended.<sup>1,6</sup>

The efficacy failure endpoint at 12 months included treated biopsy proven acute rejection (tBPAR), graft loss, death or loss to follow-up by month 12. Loss to follow-up represented patients who did not experience tBPAR, death or graft loss, and whose last contact date was prior to the 12-month visit. Study results showed that Zortress plus reduced-exposure tacrolimus was comparable to standard-exposure tacrolimus with respect to efficacy failure. The incidence of efficacy failure was lower in the Zortress plus reduced-exposure tacrolimus group compared to the tacrolimus control group at month 12 (9% vs. 13.6%, respectively). The difference in rates (Zortress vs. control) with 97.5% CI for the efficacy failure endpoint was -4.6% (-11.4%, 2.2%) and the difference in rates for the graft loss, death or loss to follow-up endpoint was -0.1% (-5.4%, 5.3%).<sup>1</sup>

The main safety objective was evolution of renal function. The estimated mean glomerular filtration rate for the Zortress plus reduced-exposure tacrolimus group was 80.9 mL/min/1.73m<sup>2</sup> and the tacrolimus control group was 70.3 mL/min/1.73m<sup>2</sup> at 12 months post-transplant in the intent-to-treat (ITT) population.<sup>1</sup>

#### Important Safety Information for Zortress (everolimus) Tablets

Only physicians experienced in immunosuppressive therapy and management of transplant patients should use Zortress. Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression. Use of Zortress may result in increased risk of kidney graft thrombosis. Reduced doses of cyclosporine are required for use in combination with Zortress in order to reduce nephrotoxicity. Zortress was associated with increased mortality in a heart transplant clinical trial. Use in heart transplantation is not recommended.

Potential serious adverse reactions associated with Zortress include hypersensitivity reactions, lymphomas and other malignancies, serious infections, kidney graft thrombosis, hepatic artery thrombosis, Zortress and CNI-induced nephrotoxicity, increased mortality in heart transplantation, angioedema, wound healing/fluid accumulation, interstitial lung disease/non-infectious pneumonitis, hyperlipidemia, proteinuria, polyoma virus infections, thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TMA/TTP/HUS), new onset diabetes after transplantation and male infertility. Live immunizations should be avoided.

The most common (incidence greater than or equal to 20%) adverse reactions in kidney transplant patients are: peripheral edema, constipation, hypertension, nausea, anemia, urinary tract infections and hyperlipidemia. The most common (incidence >10%) adverse reactions in liver transplant patients are: diarrhea, headache, peripheral edema, hypertension, nausea, pyrexia (fever), abdominal pain and leukopenia.

Please see US prescribing information at: <http://www.pharma.us.novartis.com/products/zortress.shtml>.

#### About Zortress (everolimus)

Everolimus is one of the most-extensively studied immunosuppressants in solid organ transplantation with more than 10,000 transplant recipients enrolled in Novartis-sponsored clinical trials worldwide.<sup>7</sup> Under the trade name Certican<sup>®</sup>, it is approved in more than 90 countries to prevent organ rejection for renal and heart transplant patients, and in addition, is approved in the EU and other countries worldwide to prevent organ rejection for liver transplant patients. In the US, under the trade name Zortress<sup>®</sup>, the drug is approved for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant, and is also approved in adult patients following a liver transplant.

Everolimus is also available from Novartis in different dosage strengths and for different uses in non-transplant patient populations under the brand names Afinitor<sup>®</sup> and Votubia<sup>®</sup>. It is also exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Not all indications are available in every country. As an investigational compound, the safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

#### Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "commitment," "will," "potential" or similar expressions, or by express or implied discussions regarding potential new indications or labeling for everolimus, or regarding potential future revenues from everolimus. 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 everolimus to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that everolimus will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that everolimus will achieve any particular levels of revenue in the future. In particular, management's expectations regarding everolimus 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; unexpected manufacturing issues; 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.

#### About Novartis

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets innovative prescription drugs used to treat a number of diseases and conditions, including cardiovascular, dermatological, central nervous system, bone disease, cancer, organ transplantation, psychiatry, infectious disease and respiratory. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2012, the Group achieved net sales of USD 56.7 billion, while R&D throughout the Group amounted to approximately USD 9.3 billion (USD 9.1 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 128,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit <http://www.novartis.com>.

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartis>.

#### References

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