



NEWS RELEASE

U.S. FDA Approves YONDELIS® (trabectedin) for the Treatment of Patients with Unresectable or Metastatic Liposarcoma or Leiomyosarcoma, Two Common Subtypes of Soft Tissue Sarcoma

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HORSHAM, PA, October 23, 2015 - Janssen Biotech, Inc. today announced the U.S. Food and Drug Administration (FDA) has approved YONDELIS® (trabectedin) for the treatment of patients with unresectable (unable to be removed with surgery) or metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) who received a prior anthracycline-containing regimen. The approval was based on recently published clinical efficacy and safety data from the Phase 3, randomized, open-label, controlled study (ET743-SAR-3007), which evaluated YONDELIS versus the chemotherapy agent dacarbazine, in patients with unresectable or metastatic LPS or LMS previously treated with an anthracycline and at least one additional chemotherapy regimen.¹

While approved for both LPS and LMS, YONDELIS is the first treatment to be specifically approved for LPS in the U.S.

"Our academic teams are dedicated to finding new treatments with scientific merit and the promise to improve outcomes for patients with sarcomas. Today's announcement marks a meaningful event built upon years of research, offering new hope for people living with two of the most prevalent subtypes of this serious disease - liposarcoma and leiomyosarcoma - where there are limited available alternatives," said George D. Demetri, M.D.,† Director of the Ludwig Center at Harvard and Director of the Center for Sarcoma and Bone Oncology at the Dana-Farber Cancer Institute, and principal investigator of the Phase 3 registration trial. "In the clinical trial, YONDELIS significantly increased progression free survival compared to dacarbazine; this is an important endpoint for these patients, in whom rapid worsening of the disease can lead to worse symptoms and life-threatening situations."

The pivotal Phase 3 study enrolled over 500 patients and demonstrated an improvement in progression free survival (PFS) for patients treated with YONDELIS. The median PFS among the YONDELIS treatment group was 4.2 months (n=345; 95% confidence interval (CI): 3.0 - 4.8 months), while the median PFS in the dacarbazine treatment group was 1.5 months (n=173; 95% CI: 1.5 - 2.6 months), representing a 45% reduction in the risk of disease progression or death with YONDELIS (HR=0.55; 95% CI: 0.44 - 0.70; p<0.001). The final analysis of overall survival (OS) demonstrated a median OS of 13.7 months for the YONDELIS arm and 13.1 months in dacarbazine arm, which was not significant (HR=0.93; 95% CI: 0.75, 1.15; p=0.49).

LPS and LMS are subtypes of soft tissue sarcoma (STS) and represent more than 35% of all STS cases.² LMS is an aggressive type of STS where smooth muscle cells become cancerous. LMS typically occurs in the uterus, abdominal cavity or blood vessels but can also arise in any part of the body.^{3,4} LPS is comprised of several subtypes and develops in fat cells that become cancerous in any part of the body.^{5,6}

Since YONDELIS was first approved in Europe in 2007, approximately 50,000 patients in close to 80 countries have benefited from this therapy across all indications. "The U.S. approval for YONDELIS exemplifies our commitment to improving the health of people living with cancer and addressing unmet needs," said Roland Knoblauch, M.D., Ph.D., Clinical Leader, YONDELIS, Janssen Research & Development, LLC. "We are proud that our Phase 3 study is the largest ever conducted in this patient population and we're delighted that patients in the U.S. can now benefit from the treatment."

The safety profile of YONDELIS in the Phase 3 study was consistent with previous clinical studies. The most serious risks associated with YONDELIS are neutropenic sepsis (severe infections due to decreased white blood cells), rhabdomyolysis (severe muscle problems), cardiomyopathy (heart muscle problems, including heart failure), hepatotoxicity (liver problems, including liver failure), anaphylaxis, and extravasation (leakage of YONDELIS out of the vein during infusion) leading to tissue necrosis (tissue cell damage or death) and embryofetal toxicity. Among the 378 patients who received at least one dose of YONDELIS in the randomized trial, the most common (≥20%) adverse reactions were nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%) and headache (25%). The most common (≥5%) Grade 3-4 laboratory abnormalities were neutropenia (43%), increased alanine transaminase (ALT) (31%), thrombocytopenia (21%), anemia (19%), increased aspartate aminotransferase (AST) (17%) and increased creatine phosphokinase (6.4%).

The recommended dose of YONDELIS is 1.5 mg/m² administered as an intravenous infusion over 24 hours through a central venous line every 21 days (3 weeks) until disease progression or unacceptable toxicity in patients with normal bilirubin and AST or ALT, less than or equal to 2.5 times the upper limit of normal.

Access to YONDELIS

Janssen is committed to helping patients obtain access to our medicines by offering comprehensive access services and support for patients. Janssen CarePath offers a variety of access, education, and adherence tools for providers and patients for YONDELIS, including helping to assess insurance coverage and identify cost support options. In addition, the Janssen CarePath Savings Program is available to help eligible commercial patients with their medication out-of-pocket costs. Janssen CarePath and the Janssen CarePath Savings Program are available to U.S. patients only. For more information, patients and providers can visit www.YONDELIS.com, which will be available soon.

Important Safety Information

CONTRAINDICATIONS - YONDELIS is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378). Median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). Median time to complete resolution of neutropenia was 13 days (range: 7 days to 5.0 months). Febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ with Grade 3 or 4 neutropenia) occurred in 18 patients (5%). Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%). Assess neutrophil count prior to administration of each dose of YONDELIS and periodically throughout the treatment cycle. Withhold YONDELIS for neutrophil counts of less than 1500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS for life-threatening or prolonged, severe neutropenia in the preceding cycle.

Rhabdomyolysis - YONDELIS can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). Median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). Median time to complete resolution was 14 days (range: 5 days to 1 month). Assess CPK levels prior to each administration of YONDELIS. Withhold YONDELIS for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS for rhabdomyolysis.

Hepatotoxicity, including hepatic failure, can occur. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels $> 2.5 \times$ ULN were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378). Median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3 to 4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. Assess LFTs prior to each administration of YONDELIS. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality

Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS was 5.3 months (range: 26 days to 15.3 months). Assess left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS and at 2- to 3-month intervals thereafter until YONDELIS is discontinued. Withhold YONDELIS for LVEF below lower limit of normal. Permanently discontinue YONDELIS for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks

Extravasation Resulting in Tissue Necrosis - Extravasation of YONDELIS, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS. Administer YONDELIS through a central venous line.

Embryofetal Toxicity - Based on its mechanism of action, YONDELIS can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS

Adverse Reactions - The most common ($\geq 20\%$) adverse reactions are nausea(75%), fatigue(69%), vomiting(46%), constipation(37%), decreased appetite(37%), diarrhea(35%), peripheral edema(28%), dyspnea(25%), headache(25%)

The most common ($\geq 5\%$) grades 3-4 laboratory abnormalities are: neutropenia(43%), increased ALT(31%), thrombocytopenia(21%), anemia(19%), increased AST(17%), and increased creatine phosphokinase(6.4%)

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors - Avoid use of strong CYP3A inhibitors(e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS. Avoid taking grapefruit or grapefruit juice. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS infusion, and discontinue it the day prior to the next YONDELIS infusion.

Effect of Cytochrome CYP3A Inducers - Avoid administering strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) to patients who are taking YONDELIS.

About YONDELIS (trabectedin)

YONDELIS (trabectedin) is a synthetically produced anti-tumor agent, originally derived from the sea squirt *Ecteinascidia turbinata*. It works by binding to the DNA of cancer cells and disrupting their normal cell activity, which causes cell death. More information, including the full prescribing information, will be available soon on www.YONDELIS.com.

YONDELIS is approved in close to 80 countries in North America, Europe, South America and Asia.

Under a licensing agreement with PharmaMar, Janssen Products, LP has the rights to develop and sell YONDELIS globally except in Europe, where PharmaMar SA holds the rights, and in Japan, where PharmaMar has granted a license to Taiho Pharmaceutical Co., Ltd.

About Janssen Biotech, Inc.

Janssen Biotech, Inc. redefines the standard of care in immunology, oncology, urology and nephrology. Built upon a rich legacy of innovative firsts, Janssen Biotech has delivered on the promise of new treatments and ways to improve the health of individuals with serious disease. Beyond its innovative medicines, Janssen Biotech is at the forefront of developing education and public policy initiatives to ensure patients and their families, caregivers, advocates and health care professionals have access to the latest treatment information, support services and quality care.

Janssen Biotech, Inc. and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson. For more information on Janssen Biotech, Inc. or its products, visit www.janssen.com. Follow us on Twitter at www.twitter.com/JanssenUS.

Janssen in Oncology

In oncology, our goal is to fundamentally alter the way cancer is understood, diagnosed and managed, reinforcing our commitment to the patients who inspire us. In looking to find innovative ways to address the cancer challenge, our primary efforts focus on several treatment and prevention solutions. These include a focus on hematologic malignancies, prostate cancer and lung cancer; cancer interception with the goal of developing products that interrupt the carcinogenic process; biomarkers that may help guide targeted, individualized use of our therapies; as well as safe and effective identification and treatment of early changes in the tumor microenvironment. Please visit www.janssen.com.

† Disclaimer: Dr. Demetri serves as national principal investigator of this Janssen-sponsored clinical study; he has served as an unpaid advisor to Janssen in studying the compound trabectedin. Separately, Dr. Demetri has served as a consulting advisor to Janssen with de minimus consulting fees as reviewed and permitted by the Dana-Farber Cancer Institute and Harvard Medical School. Dr. Demetri does not have any personal financial interest in the company nor in YONDELIS.

¹Demetri G, et al. Journal of Clinical Oncology. 2015; Available at:

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²Toro JR, et al. Int J Cancer. 2006;119:2922-2930.

³SARC. Soft Tissue Sarcoma Subtypes. Available at: <http://www.sarctrials.org/soft-tissue-sarcoma>. Last accessed October 2015.

⁴The Liddy Shriver Sarcoma Initiative. An Introduction to Leiomyosarcoma of the Bone and Soft Tissue. Available at: <http://sarcomahelp.org/leiomyosarcoma.html>. Accessed: October 2015.

⁵The Liddy Shriver Sarcoma Initiative. What is Liposarcoma? Available at:

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⁶University of Rochester Medical Center. Liposarcoma. Available at:

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