

PharmaMar submits registration dossier to the EMEA for Yondelis® for treatment of relapsed ovarian cancer

- ***PharmaMar today submitted the registration dossier to the European Medicines Agency (EMA) for Yondelis® (trabectedin) administered with DOXIL/Caelyxⁱ for the treatment of relapsed ovarian cancer (ROC)***
- ***PharmaMar's licensee, Ortho Biotech Products, L.P. announced the submission of an NDA to the U.S. Food and Drug Administration (FDA) for Yondelis® administered with DOXIL®/Caelyx™ for the treatment of relapsed ovarian cancer on November 20***
- ***The decision of the EMA on the approval of Yondelis® in relapsed ovarian cancer may take place in mid-2009***
- ***Epithelial ovarian cancer accounts for 4% of all female cancers in the western world with an estimated 205,000 new cases diagnosed in 2006 worldwide. It is the leading cause of death due to gynecological cancers. Over 125,000 women die from this disease each year worldwide***

Madrid, December 4th 2008: PharmaMar announced today the submission of a registration dossier to the European Medicines Agency (EMA) for Yondelis® (trabectedin) when administered in combination with DOXIL®/Caelyx™ (pegylated liposomal doxorubicin) for the treatment of women with relapsed ovarian cancer (ROC). If approved, Yondelis® combined with DOXIL®/Caelyx™ will provide a new, non-platinum treatment option for these patients Europe.

The application follows the completion of a multicenter, randomized Phase III study, OVA-301, one of the largest studies conducted in ROC, comparing the combination of Yondelis® and DOXIL®/Caelyx™ to DOXIL®/Caelyx™ alone in 672 patients. The study showed that patients treated with the combination treatment had a statistically significant improvement in the primary endpoint of progression-free survival (PFS, or the length of time during and after treatment in which the disease does not progress) compared to patients treated with DOXIL®/Caelyx™ alone.

Relapsed ovarian cancer refers to epithelial carcinoma of the ovary that recurs after treatment. According to the National Cancer Institute (NCI), it is estimated that 21,650

ⁱ The trademark of pegylated liposomal doxorubicin is DOXIL in the US and CAELYX in the EU



women will be diagnosed with, and 15,520 women will die from ovarian cancer in the U.S. in 2008. Approximately 75 percent of cases are diagnosed at an advanced stage.ⁱⁱⁱ

According to the agreement between PharmaMar – a subsidiary of Zeltia, S.A- and Ortho Biotech Products, L.P. –a subsidiary of Johnson & Johnson- , under which Yondelis is developed, PharmaMar has the rights to market Yondelis® in Europe (including Eastern Europe) and Japan while Ortho Biotech Products, L.P. has rights to market Yondelis® in the rest of the world.

Yondelis® has been designated orphan drug for the treatment of soft tissue sarcomas and ovarian cancer in the European Union, United States, and Switzerland. PharmaMar commercializes Yondelis® in the EU for the treatment of soft tissue sarcoma in adults, after failure of standard treatment.

About the OVA-301 Study

Patients were enrolled at 124 centers in 21 countries. Per the study protocol, the data were evaluated by a blinded, independent radiology review and a blinded, independent oncology review. The trabectedin/DOXIL®/Caelyx™ combination demonstrated a statistically significant improvement in PFS compared to DOXIL®/Caelyx™ alone (median PFS 7.3 versus 5.8 months, respectively) and a statistically significant reduction of 21% in the risk of progression or death during the observation period in by the independent radiology review of patients with measurable disease (HR=0.79, 95% CI (0.65;0.96), p=0.0190). This result is consistent with the results of the independent oncology review that takes into account clinical as well as imaging data in the assessment of progression. In this review, there was a 28% risk reduction for disease progression or death with the trabectedin/DOXIL®/Caelyx™ combination (HR = 0.72, 95% CI (0.60; 0.88), p = 0.0008).

Secondary endpoints included response rate, overall survival, and safety. A statistically significant increase in response rate was seen with the trabectedin and DOXIL®/Caelyx™ combination (28%) compared to DOXIL®/Caelyx™ alone (19%), as measured by the independent radiology review. A final protocol-specified survival analysis is planned after the occurrence of 520 events. The safety profile in the study was consistent with previous experience with trabectedin and DOXIL/CAELYX.

The most common adverse reactions (≥20%) for the trabectedin/DOXIL®/Caelyx™ combination compared to DOXIL®/Caelyx™ alone respectively were:

ⁱⁱ Ovarian Cancer (Invasive) Survival Rates By Race, Diagnosis year, Stage and Age. SEER Cancer Statistics review 1975-2005. National Cancer Institute, Bethesda, MD. Available at <http://seer.cancer.gov/csr/1975-2005/>

- Hematological reactions including neutropenia (77% versus 38%, with febrile neutropenia occurring in 8% of the cases and sepsis in 1% of the cases), leucopenia (48% versus 26%), anemia (48% versus 25%) and thrombocytopenia (36% versus 8%).
- Gastrointestinal reactions including nausea (74% versus 42%), vomiting (56% versus 30%) and diarrhea (26% versus 19%)
- Liver enzyme (transaminase) elevations were more common in the combination arm, but were generally reversible and not associated with evidence of chronic liver damage or other clinical consequences. Transaminase elevations included increased alanine aminotransferase (55% versus 9%) and increased aspartate aminotransferase (40% versus 10%)
- Fatigue (46% versus 36%)

Additionally, commonly associated DOXIL®/Caelyx™ adverse events, such as hand-foot syndrome (HFS) and stomatitis, occurred in fewer patients receiving the combination compared to DOXIL®/Caelyx™ alone (24% versus 54% and 20% versus 33%, respectively).

Ovarian cancer

Epithelial ovarian cancer accounts for 4% of cancers in women and is the fifth leading cause of death by cancer in the female population of developed countries (according to American Cancer Society [ACS], Cancer Reference Information, 2005). The mortality rate of this disease has not changed substantially over the past 50 years. The median age of women with ovarian cancer is 60, although it can occur in younger women, especially where there is a family history of the disease. Some 70% of women with ovarian cancer are diagnosed late when the disease is already in advanced stages (III and IV). While only 15% -20% of patients with advanced disease survive five or more years, survival can reach nearly 90% in patients with stage I (early) disease, and 70% for those in stage II (intermediate).

It is estimated that 205,000 new cases of ovarian cancer were diagnosed in 2006 in the world and that more than 125,000 women will die from this disease (Globocan 2005). According to the World Health Organization, the highest rates occur in the United States, Canada, Scandinavia, and Eastern Europe.

About Yondelis®

Yondelis® (trabectedin) is a novel cytotoxic antitumor agent that was originally derived from the Caribbean tunicate, Ecteinascidia turbinata ("sea squirt"). The compound is now produced synthetically. Yondelis® binds to the minor groove of DNA, interfering with cell division and genetic transcription processes and DNA repair machinery. Yondelis® is currently in Phase II and III development in ovarian cancer, breast cancer, hormone refractory prostate cancer. Also PharmaMar will start a phase III multicenter study of Yondelis® as first-line therapy in patients with tumor traslocation, Ewing's sarcoma, or not rhabdomyosarcomatose soft tissue sarcomas and other types of STS.

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PharmaMar

PharmaMar is the world-leading biopharmaceutical company of the Zeltia Group, and is committed to advancing the treatment of cancer through the discovery and development of new marine-derived medicines. PharmaMar has four novel compounds in clinical development: Yondelis® is currently being marketed in the European Union for the treatment of soft tissue sarcomas in adults after failure of standard therapy. Yondelis® is also in phase III for ovarian cancer and phase II for prostate, breast and paediatric cancers. Aplidin®, Zalypsis®, and Irvalec® are other marine-derived new agents in clinical development by PharmaMar, which also has a rich pipeline of preclinical candidates, and a strong R&D program.

Important note

PharmaMar, based in Madrid, Spain, is a subsidiary of Grupo Zeltia (Spanish Stock Exchange, ZEL) that has been listed on the Spanish Stock Exchange since 1963. This document is a press release, not a brochure. This document does not constitute nor is it part of any offer or invitation to sell or issue any application of purchase, offer, or shares subscription of the Group. Likewise, this document nor its distribution is part or can be of base for any contract or investment decision and does not constitute any kind of recommendation in relation with the shares of the Company.

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This press release is also available in the News section of www.pharmamar.com
