To: Submissions@nccn.org
Subject: YONDELIS® (trabectedin) submission

October 23, 2015
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NCCN Guidelines® Panel: Uterine Neoplasms

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® Uterine Neoplasms Panel review the enclosed analysis of efficacy and safety outcomes from the SAR-3007 study, a phase 3, randomized, open-label, multicenter study comparing trabectedin vs. dacarbazine in patients with advanced liposarcoma (LPS) or leiomyosarcoma (LMS), including uterine LMS, following prior therapy with an anthracycline and at least one additional systemic regimen.[1,2]

Specific Changes:

- Include YONDELIS® as a systemic therapy for uterine sarcoma

FDA Clearance: The FDA has approved YONDELIS® (trabectedin) for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.[3]

Rationale: A phase 3, randomized, multicenter study (SAR-3007) evaluated the use of trabectedin vs dacarbazine in patients with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) previously treated with an anthracycline and at least 1 additional systemic therapy (n=518). A total of 134 (39%) patients in the trabectedin group and 78 (45%) patients in the dacarbazine group had uterine LMS. Patients were randomized 2:1 to receive trabectedin 1.5 mg/m^2 intravenously (IV) via central venous access over 24 hours every 21 days with dexamethasone 20 mg IV as premedication or dacarbazine 1 g/m^2 IV over 20-120 minutes every 21 days. Progression-free survival (PFS) was significantly improved with trabectedin compared with dacarbazine (median 4.2 months vs 1.5 months, respectively; HR: 0.55; P<0.001). In the uterine LMS subgroup, median PFS was 4.0 months vs 1.5 months for the trabectedin and dacarbazine groups, respectively (HR: 0.58; 95% CI, 0.41 to 0.81).The PFS treatment benefit with trabectedin was consistently observed across all 19 preplanned subgroups examined in sensitivity analyses.[1]

At final analysis (N=577) of overall survival (OS; 381 survival events), the primary endpoint, median OS was 13.7 months in the trabectedin group vs 13.1 months in the dacarbazine group (hazard ratio [HR]: 0.927; 95% confidence interval[CI], 0.748 to 1.150; P=0.4920). In this analysis, 144 (37.5%) patients in the trabectedin group and 88 (45.6%) patients in the dacarbazine group had uterine LMS.[2] Overall survival was not reported separately for the uterine LMS subgroup.

The most common (≥20%) adverse reactions reported in the YONDELIS® Prescribing Information are nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common (≥ 5%) grades 3-4 laboratory abnormalities are: neutropenia, increased ALT, thrombocytopenia, anemia, increased AST, and increased creatine phosphokinase (CPK).[3] In the SAR-3007 study, the most common

adverse events reported were primarily grade 1-2. Grade 3-4 toxicities were primarily observed in laboratory-based measures of myelosuppression (in both treatment groups) and transient transaminase elevations (in the trabectedin group). Grade 3-4 creatine phosphokinase (CPK) elevations were seen with trabectedin treatment (5.3% vs 0.6% in the dacarbazine group), and 1.2% of patients who received trabectedin experienced rhabdomyolysis.[1] Safety results are not described separately for the uterine LMS subgroup.

The following study publications are submitted with the YONDELIS® (trabectedin) Full Prescribing Information:

> Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized, mulitcenter clinical trial. *J Clin Oncol.* 2015;33:Epub ahead of print. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.62.4734.
>
> Patel, SR, von Mehren M, Reed D, et al. Final overall survival (OS) analysis of the randomized phase-3 study of trabectedin (T) or dacarbazine (D) for the treatment of patients with advanced leiomyosarcoma (LMS) or liposarcoma (LPS). Data presented at the 18th European Cancer Congress (ECCO) organized by European Society of Medical Oncology (ESMO); September 25-29, 2015; Vienna, Austria. Asbstract 3403.

Additional relevant phase 2 study data have been published:

> Monk BJ, Blessing JA, Street DG, et al. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. *Gynecol Oncol.* 2012;124(1):48-52.
>
> Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol.* 2015;16(4):457-464.

Sincerely,

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[1]Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized, mulitcenter clinical trial. *J Clin Oncol.* 2015;33:Epub ahead of print.
http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.62.4734

[2]Patel, SR, von Mehren M, Reed D, et al. Final overall survival (OS) analysis of the randomized phase-3 study of trabectedin (T) or dacarbazine (D) for the treatment of patients with advanced leiomyosarcoma (LMS) or liposarcoma (LPS). Data presented at the 18th European Cancer Congress (ECCO) organized by European Society of Medical Oncology (ESMO); September 25-29, 2015; Vienna, Austria. Asbstract 3403.

[3]YONDELIS® (trabectedin) [package insert]. Horsham, PA: Janssen Biotech, Inc. Oct 2015.