

**Medical Officer Consult
Office of Oncology Drug Products
Division of Oncology Drug Products**

BLA #	125197
Request	Labeling Consult
Drug	Provenge (sipuleucel-T)
BLA Sponsor	Dendreon
Primary Reviewer	Y Max Ning, MD, PhD Gwynn Ison, MD
Team Leader	V. Ellen Maher, MD
Date of Consult	2/24/10
Date Consult Completed	3/10/10

Specific questions

1. The proposed indication statement reads: “PROVENGE® is indicated for the treatment of men with metastatic castrate resistant (hormone refractory) prostate cancer.” The sipuleucel-T phase 3 studies enrolled patients with asymptomatic or minimally symptomatic “Metastatic Androgen Independent Prostatic Adenocarcinoma.” The taxotere phase 3 prostate cancer studies enrolled patients with symptomatic disease many of whom were receiving narcotic analgesics. The label states “TAXOTERE in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.” Should the sipuleucel-T indication specify that the patients are minimally symptomatic? What is the current correct terminology for hormone refractory prostate cancer?

OODP Response:

The term “castrate resistant” is the most commonly used term to describe the disease setting studied in the Phase 3 trial of PROVENGE.

Indication statements typically state the underlying disease and the extent of prior therapy. These are supported by trials which have shown an effect, such as an improvement in overall survival, on the patient’s underlying disease. A statement that patients were asymptomatic or minimally symptomatic is then included in the Clinical Studies section. Indications which are supported by trials that have examined an effect on the patient’s symptoms, such as the decrease in pain intensity seen with mitoxantrone, do include these symptoms in their indication statement. On the other hand, the trial that supported the approval of Taxotere for metastatic castrate-resistant prostate cancer (mCRPC) included both asymptomatic and symptomatic patients and the approved indication reflects the population studied. As such, the indication for PROVENGE should specify the study patient population in which the key trial supporting this BLA was conducted.

2. Section 12 on clinical pharmacology includes exploratory studies and speculative statements. Section 14 (clinical studies) contains a lot of detail which we propose to remove. The proposed revised label (V2-2.23.10) with tracked changes is attached. Please comment on the proposed changes.

OODP Response:

Since our consultation is limited only to the proposed label, we cannot make any specific recommendations on the overall efficacy and safety claims as shown in the product label. Please see the following suggested changes and comments for the proposed label:

- 1. Section 12 (Clinical Pharmacology): If data are not available to support the following statement, we recommend deleting it from the PI: “During ex vivo culture with PAP-GM-CSF antigen, APCs are activated to take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface.”**
- 2. Section 14 (Clinical Studies) should focus primarily on the key study (IMPACT). Key baseline information relevant to the described efficacy findings should be included along with a statement that patients were minimally symptomatic or asymptomatic. The primary and secondary endpoints should be described clearly in the section as originally defined in the study protocol.**
- 3. Post-hoc or other exploratory analyses generally are not considered substantial evidence and therefore should be removed from the label. If you choose to include the two supportive studies, you should highlight the results of the prespecified endpoints of the studies instead of the exploratory analysis results. You may wish to provide this information after stating the outcome of the IMPACT study.**