Sipuleucel-T (Provenge)

Manufacturer: Dandreon, Inc., Seattle, Wash.

Indication: Sipuleucel-T is intended for men with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer.

Description: Sipuleucel-T is the first in a new therapeutic class known as autologous cellular immunotherapies. Cells are taken from the tumor and incorporated into a product consisting of the patient’s own blood cells and Dendreon’s fusion protein—prostatic acid phosphatase (PAP)/granulocyte–monocyte colony-stimulating factor (PAP-GM-CSF). The active components are autologous antigen-presenting cells (APCs) and PAP-GM-CSF. During culture, the recombinant antigen can bind to and can be processed by APCs into smaller protein fragments. The recombinant antigen is designed to target APCs and may help direct the immune response to PAP, an antigen expressed in prostate cancer tissue. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final sipuleucel-T product.

The cellular composition of sipuleucel-T is dependent on the composition of cells obtained after the patient undergoes leukapheresis. In addition to APCs, the final product contains T cells, B cells, natural killer (NK) cells, and other cells. The number of cells present and the cellular composition of each sipuleucel-T dose vary. This process activates the patient’s immune cells against prostate cancer cells.

Uniqueness of Product: Sipuleucel-T is composed of autologous peripheral blood mononuclear cells (including APCs) that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF. PAP is linked to GM-CSF, an immune cell activator. The patient’s peripheral blood mononuclear cells are obtained during standard leukapheresis approximately three days before the infusion date.

Warnings and Precautions:

Acute infusion reactions. Fever, chills, dyspnea, hypoxia, bronchospasm, nausea, vomiting, fatigue, hypertension, and tachycardia have occurred within one day of the infusion. In controlled clinical trials, an acute reaction developed in 71.2% of patients receiving the study drug. The most common events (at a rate of 20% or more) were chills, fever, and fatigue. In 95.1% of patients reporting acute reactions, events were mild or moderate. Fever and chills generally resolved within two days (71.9% and 89%, respectively).

In clinical trials, severe (grade 3) acute infusion reactions were reported in 3.5% of patients receiving sipuleucel-T. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle aches, nausea, and vomiting.

The incidence of severe adverse events was greater following the second infusion (2.1%), compared with 0.8% following the first infusion, and decreased to 1.3% following the third infusion. Some patients in the sipuleucel-T group (1.2%) were hospitalized within one day of the infusion because of an acute reaction. No grade 4 or 5 acute reactions were reported in the sipuleucel-T patients.

Patients with cardiac or pulmonary conditions should be closely monitored. In the event of an acute infusion reaction, the infusion rate may be decreased or stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

Precautions for controlling infectious disease. Sipuleucel-T is not routinely tested for transmissible infectious diseases; therefore, the leukapheresis material and sipuleucel-T may carry the risk of transmitting infectious diseases to health care professionals who handle the product. Accordingly, universal precautions should be used during the handling of leukapheresis material or sipuleucel-T.

Concomitant chemotherapy or immunosuppressive therapy. The use of chemotherapy (e.g., docetaxel [Taxotere, Sanofi-Aventis]) or immunosuppressive agents (e.g., systemic corticosteroids), given concurrently with leukapheresis or with sipuleucel-T, has not been studied. Sipuleucel-T is designed to stimulate the immune system, and the concurrent use of immunosuppressive agents may alter its efficacy or safety. Patients should be carefully evaluated to determine whether it is appropriate to reduce or discontinue immunosuppressive agents before treatment with sipuleucel-T.

Docetaxel plus prednisone is approved to treat androgen-independent prostate cancer that has stopped responding to hormonal therapy. Docetaxel was the first agent to have a positive effect for men with advanced cancer. It is considered the standard of care for treating metastatic, hormone-refractory prostate cancer because it has been able to improve quality of life by reducing pain and extending life.

Product safety testing. Sipuleucel-T for infusion is approved based on microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with two-day incubation to determine absence of microbial growth. The final sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination, the leukapheresis setup and the leukapheresis material and sipuleucel-T are discarded. The company notifies the treating physician.

Dosage and Administration: The recommended course of therapy consists of three complete doses, given at approximately two-week intervals. In controlled clinical trials, the median dosing interval between infusions was two weeks (range, 1 to 15 weeks). The maximum dosing interval has not been established. If the patient is unable to receive a scheduled infusion of sipuleucel-T, an additional leukapheresis procedure is necessary in order to continue the course of treatment.
Patients should be advised of this possibility before treatment begins. Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54-positive cells activated with PAP-GM-CSF.

To minimize the potential for acute infusion reactions, health care practitioners should use oral premedication with acetylsalicylic and an antihistamine approximately 30 minutes before administering sipuleucel-T.

**Commentary:** The approval of sipuleucel-T (Provenge), the first autologous cellular immunotherapy, represents a significant advance for the treatment of prostate cancer that has been refractory to standard hormonal treatment. It is likely that cancer immunotherapies will create an entirely new treatment paradigm in the future.

Sipuleucel-T is produced from the patient’s own cells; thus, the cells cannot be stored, and specialized manufacturing facilities must be available. The drug’s approval was based on the results of the phase 3, placebo-controlled Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. In that study, men with castration-resistant prostate cancer and who had been refractory to standard hormonal treatment. It is likely that cancer immunotherapies will create an entirely new treatment paradigm in the future.

Severe allergic reactions have been reported following polidocanol use, including anaphylactic or allergic reactions that result can be treated.

**Accidental intra-arterial injection.** Intra-arterial injection can cause severe necrosis, ischemia, or gangrene. If this occurs, a vascular surgeon should be consulted immediately.

**Inadvertent perivascular injection.** Pain can result with an inadvertent perivascular injection of polidocanol. If pain is severe, a local anesthetic without adrenaline may be injected.

**Dosage and Administration:** The product is intended for IV use only. For spider veins (smaller than 1 cm in diameter), polidocanol 0.5% is used. For reticular veins (1 to 3 mm in diameter), polidocanol 1% is used. A dose of 0.1 to 0.3 mL per injection, but no more than 10 mL per session, should be used. After the session, the patient should be encouraged to walk for 15 to 20 minutes. Patients should be closely observed so that any anaphylactic or allergic reactions that occur can be detected.

Compression should be maintained for two to three days after spider veins are treated and for five to seven days after reticular veins are treated. For extensive varicosities, a longer treatment with compression bandages or a higher-gradient compression stocking is recommended. Post-treatment compression is necessary to reduce the risk of deep vein thrombosis (DVT).

Treatments may need to be repeated one to two weeks later if more than 10 mL is required.

**Commentary:** Varicose veins occur when the tiny valves inside the veins stop working, interfering with the normal flow of blood. This can cause swelling, discoloration, and discomfort. When injected into the affected vein, polidocanol (Asclera) irritates the vein’s interior lining, causing it to harden and close. Blood is prevented from flowing into the malfunctioning veins, and swelling, bulging, and discomfort are eliminated. Polidocanol is not indicated for varicose veins larger than 4 mm in diameter. Spider veins, although they are not typically associated with painful side effects, can appear dark red, blue, or purple.

Most men and women with reticular or spider veins are considered good candidates for injection sclerotherapy. However, some medications or health conditions may preclude treatment, including cardiovascular disease, bleeding disorders, and pregnancy.

Most patients show improvement in appearance and symptoms soon after treatment, often after one to three sessions. The number of treatments required for optimal results may vary.

All sclerosing agents are associated with certain risks, including scarring, tissue damage, and infection.

**Sources:** www.asclera.com; http://origin-qps.onstreammedia.com/origin/multivuarchive/ENR/FX-MM92062-20100423-1.pdf

**Imiquimod Cream 3.75% (Zyclara Cream)**

**Manufacturer:** Graceway Pharmaceuticals LLC, Bristol, Tenn.

**Indication:** Imiquimod cream is indicated for the topical treatment of clinically typical, visible, or palpable actinic keratoses of the face or balding scalp in immunocompetent adults.

**Description:** The chemical formula of imiquimod is 1-(2-
methylpropyl]-1H-imidazo[4,5-c]quinolin-4-amine. The molecular formula is C_{14}H_{16}N_{4}, and the molecular weight is 240.3.

**Uniqueness of Drug:** Imiquimod is an immune response modifier that shows both antitumor and antiviral activity in vivo. The exact mechanism of action in the drug’s stimulation of the immune system is not known. However, imiquimod activates immune cells through toll-like receptor 7 (TLR7), commonly involved in pathogen recognition, on the cell surface. Imiquimod is a TLR7 agonist that activates immune cells. Topical application of the product to skin is associated with an increase in markers for cytokines and immune cells.

**Warnings and Precautions:**

**Local skin reactions.** Intense local skin reactions, including skin weeping or erosion, can occur after a few applications of imiquimod cream, and the regimen may need to be interrupted. The cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft-versus-host disease.

Administration of imiquimod cream is not recommended until the skin has healed from any other previous drug or surgical treatment. The concomitant use of imiquimod and any other imiquimod cream (e.g., Aldara Cream 5%, 3M) in the same treatment area should be avoided because this interaction might increase the risk and severity of local skin reactions.

**Systemic reactions.** Flu-like signs and symptoms may accompany, or may even precede, local skin reactions. These reactions may include fatigue, nausea, fever, myalgias, arthralgias, and chills. Interrupting the regimen and assessing the patient should be considered.

Lymphadenopathy occurred in 2% of subjects treated with imiquimod cream. This reaction resolved in all subjects by four weeks after the completion of treatment. The safety of the concomitant use of imiquimod cream and any other imiquimod cream (e.g., Aldara) has not been established; such use should be avoided because both products contain the same active ingredient and may increase the risk and severity of systemic reactions.

**Ultraviolet light exposure.** Exposure to sunlight (including sunlamps) should be avoided or minimized while patients are using imiquimod cream because of a concern for heightened susceptibility to sunburn. Patients should be advised to use protective clothing, such as a hat, when they are using imiquimod cream. Patients with sunburn should not use imiquimod cream until the skin has fully recovered.

Patients who receive considerable sun exposure (e.g., from their occupation) or who have an inherent sensitivity to sunlight should exercise caution while they are using imiquimod cream. In an animal photo-carcinogenicity study, the drug shortened the time to skin tumor formation. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid exposure to natural or artificial sunlight.

**Dosage and Administration:** Imiquimod cream should be applied once daily before bedtime to the skin of the affected area (face or balding scalp) for two treatment cycles of two weeks, separated by a two-week period without any treatment. The cream should be applied as a thin film to the entire treatment area and rubbed in until it is no longer visible. Up to two packets of the cream may be applied to the treatment area at each application. The cream should be left on the skin for approximately eight hours. Afterward, patients should remove the cream by washing the area with mild soap and water. The prescriber should demonstrate the proper application technique.

Patients should wash their hands before and after applying the cream. The cream should not be used in or on the lips and nostrils, and it should not be used in or near the eyes. Local skin reactions in the treatment area are common.

Imiquimod cream is packaged in single-use packets, with 28 packets supplied per box. No more than 56 packets should be prescribed for the total two-cycle treatment course. Unused packets should be discarded.

**Commentary:** Imiquimod cream 3.75% (Zyclara) shares the same active ingredient as imiquimod cream 5% (Aldara). Although the FDA has approved both topical creams for treating actinic keratoses, there are notable differences between the two. Zyclara is indicated for daily use on an accelerated six-week dosing cycle comprising two weeks of daily treatment, two weeks of non-treatment, followed by two weeks of daily treatment. Aldara is not approved for daily use; it is used for a full 16 weeks. Zyclara is also indicated for use on larger areas of skin, the full face, or the balding scalp; Aldara is restricted to a 25-cm² area of skin.

If actinic keratoses are visible on the surface of the skin, it is likely that more of them are present just below the skin’s surface. In 86% of patients in a clinical trial, Zyclara revealed them. In the study, Zyclara was used to treat both types of actinic keratoses—those found at the start of the study and those discovered during treatment. Finally, more than 40% of doctors reported that Zyclara significantly improved the appearance of the skin.

**Sources:** www.gracewaypharma.com; www.drugs.com/newdrugs/fda-approves-zyclara-imiquimod-cream-3-75-actinic-keratoses-2082.html