

Appendix 6: Proposed Labeling

The definition of the appropriate patient population for whom CDDP/epi gel would be prescribed is an important consideration for both Matrix and the FDA. We believe CDDP/epi gel is appropriate for the treatment of local-regional recurrent HNSCC in patients whose tumors are causing or have the potential to cause significant symptoms. No individual tumor should exceed 20 cm³, and the patient should not be a suitable candidate for another standard therapy including surgery, radiotherapy, or systemic chemotherapy.

Appropriate contraindications, precautions, warnings, and instructions for use will be incorporated into the package insert to ensure the product is administered correctly and used safely. Below are those sections from the draft package insert that describe the proper patient selection criteria and procedures for treatment.

CONTRAINDICATIONS

CDDP/epi gel should not be used for the treatment of any tumor that directly involves or threatens to invade the carotid or vertebral artery. In these patients, the potential risk of cerebral vascular complications, including cerebral vascular accidents, outweighs the potential benefit from tumor regression.

Patients with known hypersensitivity to any of the components in CDDP/epi gel, including cisplatin, bovine collagen, epinephrine or sulfites, should not be treated.

WARNINGS

Caution: CDDP/epi gel should only be administered by direct intratumoral injection. CDDP/epi gel MUST NOT be injected intravenously, intra-arterially, or intrathecally. Injection into or adjacent to a major blood vessel may cause bleeding, arterial vasospasm or vascular occlusion. In situations where there are complex anatomical relationships, use of imaging procedures to guide the injection of the drug may be advisable. Injection of CDDP/epi gel may involve a risk of damage to adjacent peripheral or cranial nerves (see PRECAUTIONS).

Local Reactions: Injection of CDDP/epi gel into tumors results in a high intratumoral concentration of cisplatin for an extended period of time. Expected local cytotoxic effects in the tumor and adjacent tissue may include erythema, swelling, erosion, ulceration, necrosis, eschar formation and/or bleeding. The incidence of local cytotoxic effects generally peaks 2 weeks after the start of treatment and resolves over the next 3-12 weeks. In clinical studies, many patients had these tissue conditions at baseline, although most of these were mild to moderate in severity. Following treatment with CDDP/epi gel, the overall incidence and severity of local cytotoxic reactions increased in the CDDP/epi gel group.

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However, most of these effects were mild to moderate and resolved with standard wound care measures.

Patients at risk for delayed wound healing due to prior surgery, radiation, poor nutrition or inadequate blood supply may be at higher risk for developing more severe local cytotoxic effects. In cases where administration of the next scheduled CDDP/epi gel treatment might be expected to intensify the severity of existing local cytotoxic effects, especially ulceration and necrosis, treatment with CDDP/epi gel should be delayed until there is adequate healing of the tumor or surrounding tissue (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Allergic Reactions: Anaphylactic-like reactions to platinum-containing products have been reported to occur within minutes of systemic administration in patients with prior exposure to similar compounds. The safety of CDDP/epi gel in patients with a history of anaphylaxis or a history of multiple severe allergies has not been demonstrated. Patients with a history of dietary beef allergy should be carefully evaluated before injection with products containing bovine collagen because such patients may be predisposed to allergic reaction to any bovine-derived product.

CDDP/epi gel contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and severe or even life-threatening asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and is probably low. Sulfite sensitivity is more frequent in asthmatic than in nonasthmatic people.

Pregnancy: CDDP/epi gel should not be used in patients who are pregnant, lactating or breast feeding. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin has been shown to be mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Patients should be advised to avoid becoming pregnant during CDDP/epi gel therapy. If CDDP/epi gel is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General: Not for intravenous injection. CDDP/epi gel should only be administered by direct intratumoral injection and MUST NOT be injected intravenously, intra-arterially or intrathecally (see WARNINGS).

Physicians administering this product should be familiar with the local and surgical anatomy of the site of injection. Imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) may be required prior to treatment with CDDP/epi gel in order to adequately define the local

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anatomy and to plan the approach and extent of the local injection. In some patients, imaging guidance with ultrasound or CT may assist needle placement at the site of injection.

Local injection of CDDP/epi gel involves a risk of serious adverse experiences such as hemorrhage or cerebral vascular events, especially with tumors involving major vessels of the extracranial vascular system. Tissue damage, needle trauma to the artery, chemical irritation, mechanical pressure from a large injected volume, local inflammation and swelling or tumor progression alone or in combination with CDDP/epi gel may contribute to the occurrence of cerebral vascular events.

Pain Management: A comprehensive pain management program should be planned for each patient prior to treatment. The physician should assess the patient's pain prior to injection and anticipate the possibility that pain will be increased during and following the injection of CDDP/epi gel. Sufficient time should be allowed for any anesthetic or analgesia to take effect prior to administration of CDDP/epi gel. It may be valuable to obtain consultation from an anesthesiologist or other pain-management specialist. Topical and other local anesthetics, loco-regional nerve blocks and systemic analgesics may be used alone or in combination, as appropriate. If a local anesthetic is used, it should be injected around the tumor margins. Local anesthetics containing epinephrine are contraindicated.

It should be assumed that narcotic-strength analgesia will be required at least for the first CDDP/epi gel administration procedure. Narcotic-strength analgesia with parenteral morphine sulfate, meperidine or fentanyl has been used in clinical trials of CDDP/epi gel, frequently in combination with lorazepam. An alternative regimen may involve local anesthesia with lidocaine and administration of midazolam hydrochloride. Provisions should be made to continue adequate analgesia for 24-48 hours following the procedure, during which time treatment with narcotic strength analgesics may be required. Subsequently, nonsteroidal anti-inflammatory drugs or acetaminophen may be adequate for pain management.

Wound Care: Local infection may occur, particularly in previously irradiated areas or in areas with pre-existing ulceration and necrosis, where facultative anaerobes and other pathogens may thrive. Cellulitis was reported infrequently in clinical studies. Management of local infection during CDDP/epi gel therapy, with local wound care or systemic antibiotics, may be necessary. The local cytotoxic effects of CDDP/epi gel on treated tumors may include erythema, swelling, erosion, ulceration, necrosis, eschar and/or bleeding (see WARNINGS). Patients at risk for delayed wound healing due to prior surgery, radiation, poor nutrition or inadequate blood supply may be at higher risk for developing more severe local cytotoxic effects.

Renal Effects and Dehydration: The low systemic exposure to cisplatin released from CDDP/epi gel is not expected to produce direct renal toxicity. Nevertheless, patients with advanced head and neck

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cancer frequently have poor oral intake and may be both dehydrated and poorly nourished. This may be especially true for elderly patients, who are also more likely to have decreased renal function. Oral intake may be further compromised in the days following CDDP/epi gel treatment due to the local cytotoxic effects of the drug or from anorexia associated with concurrent narcotic analgesics. In these patients, the need for adequate hydration and/or intravenous fluid replacement should be considered.

Information for Patients: Patients should be informed of the expected effects of CDDP/epi gel, in particular, the likelihood of increased pain during and after injection. Patients should also be made aware that treatment may result in local skin reactions, such as erythema, swelling, erosion, ulceration, necrosis, eschar formation and/or bleeding or a worsening of these conditions that may be present before treatment with CDDP/epi gel. These effects occur within days of treatment and may become worse as treatments proceed before improvement is noted.

Drug Interactions: No formal drug interaction studies have been conducted. In addition, the short and long-term toxicity profiles of CDDP/epi gel, when given concurrently with radiation or systemic chemotherapy, have not been studied.

DOSAGE AND ADMINISTRATION

Physicians administering this product should be familiar with the local and surgical anatomy of the site of injection. In addition, to reduce the possibility of cardiovascular complications, patient blood pressure and pulse should be monitored regularly during treatment.

Radiological imaging studies with CT, MRI, ultrasound or other specialized radiological techniques may be required to accurately identify the extent of local tumor involvement and to plan the treatment program for local tumor injection (see PRECAUTIONS).

Treat each tumor with 0.25 mL CDDP/epi gel per cm^3 of tumor volume to a maximum of 10 mL of CDDP/epi gel administered at any one visit. One or more tumors may be treated on any one treatment day. CDDP/epi gel should be administered on a weekly basis for up to 6 treatments (one cycle).

Estimate tumor volume by physical examination or imaging studies using the three tumor dimensions (length x width x height x 0.5). At each treatment visit, the tumor volume should be remeasured and the dose volume recalculated, as needed. Additional treatment cycles can be administered if the tumor progresses or as new tumors develop.

Tumors treated with CDDP/epi gel should be monitored on a weekly basis to assess the effect of treatment on tumor regression, as well as any local cytotoxic effects on the tumor and adjacent tissues (see WARNINGS). If needed, treatment should be delayed for one week or until there is adequate healing of any local cytotoxic effects in the tumor or surrounding tissue.

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Intratumoral Injection Technique: The precise anatomical localization of the tumor should be well defined by physical examination or pretreatment CT, MRI or x-ray studies. If the exact placement of injections cannot be performed by visual guidance and physical examination, imaging guidance and monitoring of the procedure with ultrasound or CT scan may be necessary. Imaging-guidance is recommended for injection of tumors that may be impinging on major arteries, especially when the local anatomy has been altered by surgery or radiation. Care should be taken in order to avoid unintentional injection of CDDP/epi gel into a blood vessel (See PRECAUTIONS).

Using a small (22 to 25 gauge) needle attached to a Luer-lock syringe, insert the needle into the base of the tumor at approximately a 45-degree angle. Pull back gently on the plunger. If blood appears, withdraw the needle and repeat. If blood does not appear, proceed with administration. Depending on the size and location of the tumor, the injection may be done by tracking the product through the tumor from a single puncture site or by injecting the tumor from multiple sites in parallel rows approximately 0.5 to 1.0 cm apart.

CDDP/epi gel contains epinephrine. To minimize any possible side effects from epinephrine, the dose volume should be injected slowly in 2 mL increments, waiting approximately 5 minutes between each 2 mL administration. The patient's blood pressure and pulse should be measured immediately following each incremental administration of CDDP/epi gel. If there are no clinically significant changes in blood pressure, pulse or any other clinically significant event, an additional 2 mL may be injected. This process should be repeated until the full dose (up to 10 mL) is administered. If, at any time during the injection procedure, the patient experiences a clinically significant change in blood pressure, pulse, clinical status or intolerable pain, the procedure should be discontinued until the following treatment visit a week later. Once the procedure has been completed, vital signs should be monitored at 15 to 30 minute intervals until all vital signs are stable and the patient has recovered from any sedation or anesthesia.