

MEDICAL OFFICER'S REVIEW MEMORANDUM

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Material Reviewed: STN125348: Proposed Fibrocell Physician Training Manual Draft Version 1.0, issued December 13, 2010.

Date of Review: June 9, 2011

Consult: Jane Liedtka, MD, Medical Officer, CDER/ODEIII/DDDP

Executive Summary: The sponsor has submitted a manual to be used as part of a sponsor-directed training program that is mandatory for all health professionals who will administer Laviv, an autologous fibroblast product intended for improvement in the appearance of nasolabial fold wrinkles. The sponsor's BLA resubmission and the proposed package insert (PI) are currently under review. At the time of this review, FDA and the sponsor have reached agreement on nearly all of the contents of the package insert. Reference to the package insert appears throughout this review of the Training Manual.

The Training Manual is generally clearly written and comprehensive. However, there are a number of statements that are discordant with those in the most recent version of the product label and may be misleading. In addition, several statements and descriptions require clarification. The following lists these items in order of appearance. These must be acceptably amended prior to approval of Laviv.

Section 1 Preface:

1.1 Line 1-2. *LAVIV® is a live cellular therapy for the treatment of moderate to severe facial wrinkles, such as nasolabial fold wrinkles.*

Change indication to match that of the PI. This needs to be fixed in other parts of the manual as well. Laviv is indicated only for nasolabial fold wrinkles, and this should be stated in the manual.

Line 9-10 *Only the fibroblast component of the skin biopsy is expanded....*

Change to "Fibroblasts represent the predominant cell type expanded ...

Line 12

Add dimethyl sulfoxide (DMSO)

Line 13

After buffered medium add "called Dulbecco's Modified Eagles Medium (DMEM)

Line 15

Change shelf life to “must be used on the day of receipt by 6pm EST”

Change storage temperatures to include Fahrenheit
Prior to use, LAVIV® “vials” must be stored on their side

LAVIV® is unlike other products used to treat wrinkles. Unlike inert fillers, the autologous fibroblasts correct, rather than replace damaged dermal and subcutaneous tissues.

This misleading, promotional statement should be deleted from the manual. The mechanism of action of Laviv is unknown.

Administration of LAVIV® can only be performed by trained and authorized physicians.

This is fine, but I am not sure how the part about physicians fits with our regulations.

Section 2 Administrative Perspectives:

For optimum results, patients should be administered multiple treatments, separated by three to six week intervals. In pivotal clinical studies, three treatments with LAVIV® administered at three to six week intervals were found to achieve a gradual reduction in nasolabial fold lines and wrinkles.

This statement should be amended to state that demonstration of clinical efficacy was based on three treatments. Otherwise, it implies that patients could receive any number more than one.

Product Expiration

Change to “The product will expire at 6:00pm EST on the day of receipt”

Section 4 Patient Selection and Preparation:

4.1 Indications:

LAVIV® is an autologous regenerative cell therapy indicated for the improvement of moderate to severe facial wrinkles (such as nasolabial fold wrinkles) in adults 2: 18 years of age.

Again, the indications are discordant with those in the label. The indications should read exactly as in the label.

4.2 – 4.3 Contraindications, Precautions, and Concurrent illness, and “Patient Education” sections: As an example,

There are no known contraindications for treatment with LAVIV®. However, the following warnings and precautions should be considered.

The contraindications should appear as written in the label:

- **Allogeneic use of LAVIV**

- **Allergy to gentamicin, amphotericin, dimethyl sulfoxide (DMSO), or material of bovine origin**
- **Active infections in the facial area**

Similarly, the entire section 4.2-4.3 should be re-written to be in precise accord with the label.

- **Hypersensitivity reactions can occur with LAVIV. (5.1)**
- **LAVIV can cause bleeding and bruising at the treatment site. (5.2)**
- **Vasculitis has occurred following treatment with LAVIV. (5.3)**
- **Herpes labialis has occurred with LAVIV treatment. (5.4)**
- **Basal cell cancer has occurred following treatment with LAVIV (5.5)**
- **Keloid and hypertrophic scarring may occur following post-auricular skin biopsies or LAVIV injections. (5.6)**
- **Patients with genetic disorders affecting dermal fibroblasts or formation of normal collagen matrices may have an abnormal response to LAVIV. (5.7)**
- **Immunosuppressed patients, or those who undergo chemotherapy for malignancies or receive immunomodulatory therapies for autoimmune diseases, may have an increased susceptibility to infection and difficulty healing from LAVIV treatments.(5.8)**
- **Employ universal precautions when handling LAVIV. Patients undergoing procedures associated with LAVIV are not routinely tested for adventitious viruses. (5.9)**
- **Sterility tests are not completed when LAVIV is shipped to the clinic. (5.10)**

Section 5 Procedures:

5.3 – Dispensing Product

Verify in particular that the identification on the “Tyvek envelope and” vial corresponds to the patient scheduled for treatment

5.4

The description of use of ice for topical anesthesia is not clear. The sponsor should specify whether the ice should be wrapped and how it is to be applied.

The description of the injection technique needs some clarification, especially the part about preventing the cells from leaking from the injection puncture by “crisscrossing” the injections. This needs clarification, probably with a diagram.

Injection site erythema, swelling, bruising and pain were reported in more than 5% of patients during clinical trials with LAVIV®, but these events typically resolved within one week.

This should be corrected to match information in the PI (see below).

The same corrections regarding ice packs should be applied to the aftercare section.

Section 6 Adverse experiences:

This section should be corrected to reflect information in the product label. The manual should list AEs occurring in $\geq 1\%$ of trial subjects. The statement regarding serious adverse events --- *No serious adverse events related to LAVN® have been reported in any controlled Clinical study conducted to date* --- should be modified to include the case of leukocytoclastic vasculitis, which may possibly be related to administration of Laviv.

From the most recent version of the PI:

The most common adverse reactions, occurring in $\geq 1\%$ of patients who received LAVIV, were injection-site redness, bruising, swelling, pain, hemorrhage, edema, nodules, papules, irritation, dermatitis, and pruritus. (6)

Adverse reactions occurring in fewer than 1% of trial subjects were acne, facial or eyelid edema, hypersensitivity or decreased skin sensations in the injection site, post-procedural discomfort (headache, toothache, and jaw pain), herpes labialis, hyperpigmentation, injection-site ischemia, basal cell cancer, and leukocytoclastic vasculitis. (6.1)

RECOMMENDATIONS: The Training Manual can be approved only after it is satisfactorily amended (see comments to sponsor).

COMMENTS TO SPONSOR¹:

The following comments have been sent to the sponsor (June 10, 2011):

Section 1 Preface:

1.1 Line 1-2. *LAVIV® is a live cellular therapy for the treatment of moderate to severe facial wrinkles, such as nasolabial fold wrinkles.*

Please change the indication to match that of the current PI. This needs to be changed in other parts of the manual as well. Laviv is indicated only for nasolabial fold wrinkles, and this should be stated in the manual.

Line 9-10 *Only the fibroblast component of the skin biopsy is expanded....*

Please change to “ Fibroblasts represent the predominant cell type expanded ...

Line 12

Please add dimethyl sulfoxide (DMSO)

Line 13

¹ These comments incorporate the issues raised in this review as well as those in the consult by Dr. Liedtka and comments by Dr Thomas at FDA.

After buffered medium add “called Dulbecco’s Modified Eagles Medium (DMEM)”

Line 15

Change shelf life to “must be used on the day of receipt by 6pm EST”

Please change storage temperatures to include Fahrenheit.

Prior to use, LAVIV® “vials” must be stored on their side

LAVIV® is unlike other products used to treat wrinkles. Unlike inert fillers, the autologous fibroblasts correct, rather than replace damaged dermal and subcutaneous tissues.

Please delete this statement from the manual. The mechanism of action of Laviv is unknown.

Section 2 Administrative Perspectives:

For optimum results, patients should be administered multiple treatments, separated by three to six week intervals. In pivotal clinical studies, three treatments with LAVIV® administered at three to six week intervals were found to achieve a gradual reduction in nasolabial fold lines and wrinkles.

This statement should be amended to state that demonstration of clinical efficacy was based on three treatments. Otherwise, it implies that patients could receive any number more than one.

Product Expiration

Please change to “The product will expire at 6:00pm EST on the day of receipt”

2.2.2 Under Treatment Supplies: Please clarify the following:

- "No dead space" syringes with 0.1 mL gradations, 0.5 to 1.0 mL- does this mean TB/tuberculin syringes? Please clarify the exact type of syringe that is referred to.
- " " should be spelled out as "inch"
- Please provide examples of aseptic cleansing solution
- Please specify whether certain supplies -such as marking pen, gauze, tape need to be sterile – Perhaps it is best to divide supplies in this list into sterile and nonsterile
- Spell out PBS.

Section 4 Patient Selection and Preparation:

4.1 Indications:

LAVIV® is an autologous regenerative cell therapy indicated for the improvement of moderate to severe facial wrinkles (such as nasolabial fold wrinkles) in adults 2: 18 years of age.

Again, the indications are discordant with those in the label. The indications should read exactly as in the label. We also request deletion of the term regenerative.

4.2 – 4.3 Contraindications, Precautions, and Concurrent illness, and “Patient Education” sections:

As an example, you state that:

There are no known contraindications for treatment with LAVIV®. However, the following warnings and precautions should be considered.

However, there are contraindications, which should appear as written in the label:

- **Allogeneic use of LAVIV**
- **Allergy to gentamicin, amphotericin, dimethyl sulfoxide (DMSO), or material of bovine origin**
- **Active infections in the facial area**

Similarly, the entire section 4.2-4.3 should be re-written to be in precise accord with the label.

- **Hypersensitivity reactions can occur with LAVIV. (5.1)**
- **LAVIV can cause bleeding and bruising at the treatment site. (5.2)**
- **Vasculitis has occurred following treatment with LAVIV. (5.3)**
- **Herpes labialis has occurred with LAVIV treatment. (5.4)**
- **Basal cell cancer has occurred following treatment with LAVIV (5.5)**
- **Keloid and hypertrophic scarring may occur following post-auricular skin biopsies or LAVIV injections. (5.6)**
- **Patients with genetic disorders affecting dermal fibroblasts or formation of normal collagen matrices may have an abnormal response to LAVIV. (5.7)**
- **Immunosuppressed patients, or those who undergo chemotherapy for malignancies or receive immunomodulatory therapies for autoimmune diseases, may have an increased susceptibility to infection and difficulty healing from LAVIV treatments.(5.8)**
- **Employ universal precautions when handling LAVIV. Patients undergoing procedures associated with LAVIV are not routinely tested for adventitious viruses. (5.9)**
- **Sterility tests are not completed when LAVIV is shipped to the clinic. (5.10)**

Section 5 Procedures:

- Under Biopsy Preparation 5.1.1, please specify in bullet 6 whether all these items need to be sterile
- Under Biopsy Technique 5.1.2 Item 4, you reference Betadine. There are several products marketed under this name, all contain povidine-iodine but some contain detergent as well. Use instructions differ among these products (the detergent-containing product must be rinsed off). We request that you use the generic name povidine-iodine, which is the active ingredient.

5.3 – Dispensing Product

Verify in particular that the identification on the "Tyvek envelope and" vial corresponds to the patient scheduled for treatment

5.4

Under Treatment Preparation: 5.4.1

- You refer to use of ice as a topical anesthetic but recommend avoiding direct skin contact. This could be confusing. Please specify that ice should be "wrapped in a cotton towel" or some similar procedure before being applied to the area to avoid affecting fibroblast growth.
- The warning regarding not using infiltrative anesthesia should be strengthened, perhaps given its own paragraph and *for* bolded.

Under Injection Technique: 5.4.2

- Bullet #8 should be clarified. You reference the "arms" of the syringe, but this term is not clear. If this term is retained, we recommend a diagram of a syringe with the "arms" marked.
- After #13: You state, "So that the cells do not leak from the injection puncture site, it is advisable to ensure the end of the needle is just slightly adjacent to the insertion point from the previous injection ("crisscross" the injections slightly)." The use of the term "crisscrossing" is not clear in this context. Suggest using a diagram to clarify.

Under Aftercare: 5.4.3

- Under #2-same comment as above about icepack
- Under #5-second bullet- same comment as above about icepack

5.4.3.5 Injection site erythema, swelling, bruising and pain were reported in more than 5% of patients during clinical trials with LAVIV®, but these events typically resolved within one week.

This should be corrected to match information in the PI for events occurring in $\geq 1\%$ of subjects (see below).

Section 6 Adverse experiences:

This section should be corrected to reflect information in the product label. The manual should list AEs occurring in $\geq 1\%$ of trial subjects. The statement regarding serious adverse events --- *No serious adverse events related to LAVN® have been reported in any controlled Clinical study conducted to date* --- should be modified to include the case of leukocytoclastic vasculitis, which may possibly be related to administration of Laviv.

For reference, from the most recent version of the PI:

The most common adverse reactions, occurring in $\geq 1\%$ of patients who received LAVIV, were injection-site redness, bruising, swelling, pain, hemorrhage, edema, nodules, papules, irritation, dermatitis, and pruritus. (6)

Adverse reactions occurring in fewer than 1% of trial subjects were acne, facial or eyelid edema, hypersensitivity or decreased skin sensations in the injection site, post-procedural discomfort (headache, toothache, and jaw pain), herpes labialis, hyperpigmentation, injection-site ischemia, basal cell cancer, and leukocytoclastic vasculitis. (6.1)