



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: May 10, 2011

From: Jane Liedtka M.D., Medical Officer, Dermatology, DDDP

Through: Jill Lindstrom M.D., Dermatology Team Leader, DDDP
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To: Yao-Yao Zhu, M.D, Medical Officer, OCTGT/DCEPT/CEB

Cc: Julie Beitz, M.D., Office Director, ODE 3, CDER

Re: DDDP Consult # 1343 STN125348

Autologous Fibroblasts Expanded Ex-Vivo, Administered Intradermally

Material Reviewed:

STN125348:

Physician Training Manual

Background

On March 6, 2009 CBER received a BLA from sponsor Isolagen Technologies Inc (now known as Fibrocell Technologies Inc) for use of IsolagenTherapy™ (now known as azficel-T), an injectable autologous cellular product composed of fibroblasts, indicated for the treatment of moderate to severe nasolabial fold wrinkles in adults.

In June of 2009 CBER consulted DDDP regarding multiple clinical issues pertaining to this BLA submission including adverse events, population, labeling language, post-

marketing surveillance, endpoints, photographic assessment and safety. The DDDP consultation report was finalized and sent to CBER in August of 2009.

A Complete Response letter was sent to the sponsor on Dec 18, 2009. A second consult was completed by DDDP on April 21, 2010. A third consult was completed on Nov 19, 2010. A fourth consult was completed on March 23, 2011. On May 2, 2011 a fifth consult was requested with the following question:

CBER requests DDDP comments regarding Physician Training Manual in the following aspects: selection and screening patients, appropriate techniques for performing biopsies, preparation of cells and product handling, instruction of injection technique, and documentation and follow-up of adverse events.

Review

See annotated version of Physician Training Manual – Attachment A

Under Treatment Supplies 2.2.2 the following are confusing

- “No dead space” syringes with 0.1 mL gradations, 0.5 to 1.0 mL-this needs explanation - do they mean “TB/tuberculin syringes-the sponsor needs to clarify what type of syringe they are referring to
- ” should be spelled out as “inch”
- Give examples of aseptic cleansing solution
- Specify whether certain supplies –such as marking pen, gauze, tape need to be sterile -maybe divide supplies in list into sterile and nonsterile

Under Biopsy Kits 3.1

- Spell out what PBS is or give an explanation in parenthesis

Under Biopsy Preparation 5.1.1

- Specify in bullet 6 whether all these items need to be sterile

Under Biopsy Technique 5.1.2

- Item #4-The sponsor references Betadine- there are several products marketed under this name, all contain povidine-iodine but some contain detergent as well. Use instructions differ between products (the detergent containing product must be rinsed off). Instead they should use the generic name povidine-iodine which is the active ingredient they are most likely wanting to reference.

Under Treatment Preparation: 5.4.1

- The sponsor references using ice as a topical anesthetic but recommends avoiding direct skin contact-this is confusing. The sponsor should specify that ice should be “wrapped in a cotton towel” or something similar before being applied to the area to avoid effecting fibroblast growth.
- The warning regarding not using infiltrative anesthesia should be strengthened-given its own paragraph and /or bolded would be options.

Under Injection Technique: 5.4.2

- Bullet #8 needs to be clarified. The sponsor references the “arms” of the syringe. Despite 15 years in dermatologic clinical practice I have never heard of a syringe having arms. If this terminology is to be used I would recommend a diagram of a syringe with the “arms” marked or different terminology used.
- After #13-the sponsor refers to “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 (“criss-cross” the injections slightly).” Not sure what they mean by “crisscrossing” - again a diagram to clarify may be helpful.

Under Aftercare: 5.4.3

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

Discussion

Overall, the Physician Training Manual is a well written, comprehensive document. I have made the above suggestions to improve clarity for the clinician.