Product: LAVIV®

Proper Name: Azficel – T

Manufacturer: Fibrocell Technologies, Inc.

Indication: Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.

Description: LAVIV is an autologous cellular product composed of fibroblasts suspended in Dulbecco's Modified Eagle's Medium (DMEM) without phenol red. Dermal fibroblasts from post-auricular skin biopsy tissue are aseptically expanded using standard tissue-culture procedures until sufficient cells for three doses are obtained.

BLA: STN BL 125348/0

Regulatory Milestone:

Isolagen Technologies, Inc (renamed Fibrocell Technologies, Inc in 2009) marketed an autologous fibroblast product, referred to as Isolagen Therapy™ (IT), as a cosmetic treatment in the United States from December 1995 to February 1999 without FDA premarket approval. IT was also marketed in the United Kingdom between 2002 and 2007. In compliance with FDA's regulation of somatic cell therapies and the requirement to file Investigational New Drug Applications (IND) and follow a formal Biologics License Application (BLA) approval process, IT was removed from the US marketplace in 1999, and clinical trials of azficel-T were initiated in 2003 under IND --(b)(4)--.

Fibrocell Technologies, Inc submitted BLA STN#125348 on March 6, 2009 to request marketing approval of azficel-T. A Cellular, Tissue, and Gene Therapies Advisory Committee (AC) meeting was held in October 2009 to discuss the safety and efficacy of azficel-T (see section 8 Advisory Committee Meeting below). The majority of AC members stated that azficel-T was shown in clinical trials to be effective for the treatment of nasolabial fold wrinkles. However, the majority also expressed concern regarding the safety of the product. Some AC members suggested that gaining knowledge of the biological activity of the product at the histological level was necessary to increase understanding of the risks associated with the product.

On December 18, 2009, FDA issued a Complete Response (CR) letter to Fibrocell Technologies, Inc, to request additional information on the manufacturing quality and controls and on the clinical safety of azficel-T. On December 22, 2010, the applicant resubmitted the BLA with complete responses to all FDA information requests in the CR letter. The December 22, 2010 amendment and subsequent amendments addressed adequately all of the outstanding issues from the FDA CR letter.

PDUFA Goal Date: June 22, 2011

FDA Approval Date: June 21, 2011

Package Insert: LAVIV® (azficel-T) Package Insert

Summary Basis for Regulatory Approval: June 20, 2011 Summary Basis for Regulatory Action, June 20, 2011 - Laviv

European Public Assessment Report: Not available

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Fibrocell Technologies, Inc.	
Transgene	-	
Indication	LAVIV® (azficel-T) is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.	1
Virus and Serotype	-	
Cell Substrate	Autologous fibroblasts	2
Manufacturing platform	It is a cellular product composed of fibroblasts suspended in Dulbecco's Modified Eagle's Medium (DMEM) without phenol red. Dermal fibroblasts from post-auricular skin biopsy tissue are aseptically expanded using standard tissue-culture procedures until sufficient cells for three doses are obtained. Cells are then cryopreserved in a protein-free solution containing DMSO.	2
Dose in vial/final container	18 million autologous fibroblasts in a 1.2 milliliters suspension, sufficient to administer 1 milliliter of product.	1
Dose / patient	0.1 milliliter per linear centimeter into the nasolabial fold wrinkles. The recommended treatment regimen is three treatment sessions at 3-6-week intervals.	1

1. Package insert: LAVIV® (azficel-T) Package Insert
2. FDA SBAR – quality: Summary Basis for Regulatory Action, June 20, 2011 - Laviv

Advisory Committee:

An FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting took place on 9th October 2009, in Bethesda, Maryland. Topics covered at the AC meeting included tumorigenicity potential of the fibroblast cell suspension; potential risk for hypertrophic scarring,

keloid formation, or abnormal pigmentation, in the non-White population; potential safety risks in patients over 65 years of age and in males; and a post-marketing training program for practitioners.

The two voting questions were the following:

1. Do the data presented demonstrate safety for the proposed indication?

    o If no, what additional studies should be performed?

    o If yes, do you have any specific recommendations for the labeling?

Discussion:

Due to a lack of data on the mechanism of action, some Committee members thought there was insufficient information to assess the safety of azficel-T. Other Committee members commented that safety might be less of a concern as this is an autologous product and the available clinical data did not suggest that the product was unsafe. However, there was general consensus that as this is a novel cellular therapy for a non-life-threatening condition, safety standards should be set at a high level. The Committee commented on the lack of sufficient data related to the processing, characterization, and collagen production of the injected cells. The Committee considered the local adverse event profile of azficel-T to be expected and manageable but had concerns regarding the underlying changes in the dermis, the fate of the cells, and tumor risks from cell transformation.

The Committee suggested that additional safety and mechanistic data could be obtained by conducting a clinical study in which azficel-T is injected into a less visible area on the body, followed by taking serial biopsies for analysis.

Safety voting: Yes: 6; No: 8

2. Do the data presented demonstrate effectiveness for the proposed indication?

    o If no, what additional studies should be performed?

    o If yes, do you have any specific recommendations for the labeling?

Discussion:

A majority of the Committee agreed that the available data demonstrated efficacy of azficel-T in the narrowly defined proposed indication: improvement in appearance of moderate to severe nasolabial fold wrinkles for six months. The Committee proposed that answers about the fate of the cells (survival, proliferation, migration, transformation), whether collagen and/or elastin were deposited at the injection site, and whether remodeling, repair or scar formation took place could be readily obtained from a post-treatment biopsy study.

Efficacy voting: Yes: 11; No: 3

After review of the original BLA submission, and consideration of the Advisory Committee recommendations, the FDA determined that the safety data presented for azficel-T in the original application were not sufficient to support approval. Therefore, the FDA's December 18, 2009 CR letter to Fibrocell required submission of the results of an additional safety study involving histological analysis of skin biopsies taken posttreatment with azficel-T or saline control.

NCT Numbers

NCT	TRIAL PHASE	SUBJECTS ENROLLED	STUDY TITLE	COUNTRIES
NCT00649428	3	203	Safety and Efficacy Study of Isolagen TherapyTM in the Treatment of Nasolabial Fold Wrinkles	United States
NCT00655356	3	218	Safety and Efficacy Study of Isolagen Therapy in the Treatment of Nasolabial Fold Wrinkles	United States
NCT00654654	2	50	Safety and Efficacy Study of Isolagen TherapyTM in Treatment of Facial Wrinkles and Creases	United States
NCT00642642	2, 3	122	Safety and Efficacy Study of Autologous Fibroblasts in the Treatment of Severe Facial Acne Scarring	United States

EudraCT Numbers: None

Publications:

- Azficel-T. (2018). In Drugs and Lactation Database (LactMed). National Library of Medicine (US).
- Smith, S. R., Munavalli, G., Weiss, R., Maslowski, J. M., Hennegan, K. P., & Novak, J. M. (2012). A multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy for the treatment of nasolabial fold wrinkles. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.], 38(7 Pt 2), 1234–1243. https://doi.org/10.1111/j.1524-4725.2012.02349.x