Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

Final Review Memorandum: GINTUIT
OBE/DE Review for Pharmacovigilance Planning
BLA STN 125400

Product: GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen) Cellular Sheet for Topical Oral Application

Indication: For the treatment gingival and alveolar mucosal surface defects in adults

Sponsor: Organogenesis, Inc.

Date: February 29, 2012

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Introduction

OBE/DE has completed a review of BLA STN 125400 for GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen), Cellular Sheet for Topical Oral Application (Organogenesis, Inc.). The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety monitoring, studies, or other pharmacovigilance activities.

Regulatory History of GINTUIT (Allogenic Cultured Keritinocytes and Fibrinoblasts in Bovine Collagen)

GINTUIT, previous known as "Apligraf (oral)" (Organogenesis Inc., Canton, MA) is a bilayered tissue-engineered skin substitute composed of a dermal layer of human fibroblasts in a bovine Type I collagen –b(4)-- and an overlying cornified epidermal layer of living human keratinocytes. The keratinocytes and fibroblasts used in GINTUIT are derived from neonatal foreskin, and their ability to produce cytokines that are involved in wound healing has been demonstrated in pre-marketing studies for Apligraf for the indication of use for cutaneous wounds. On 22 May 1998, the FDA/CDRH approved Apligraf as a Class III medical device for the treatment of venous leg ulcers (VLU; P950032). On 20 June 2000, a supplement was approved for the treatment of diabetic foot ulcers (DFU; P950032/S016). Between May 22, 1998 and August 31, 2011, approximately –b(4)-- commercial units of Apligraf were distributed. Prior to US licensure, Apligraf was originally approved in Canada in 1997, and has distribution in several other countries, including Switzerland. Organogenesis has sponsored 19 clinical trials (totaling 787 patients) to evaluate acute and chronic wound indications including: VLU, DFU, skin graft donor sites, acute cutaneous wounds (including those resulting from excisions), acute full-thickness wounds post-excision of burns (--------b(4)----------), oral mucosal wounds, chronic pressure ulcers, and wounds due to epidermolysis bullosa. (BLA module 2:,2.2-Introduction)

While the precise mechanism of action of GINTUIT is still unknown, the product is believed to improve the rate and quality of healing by secondary intention (BLA module 2:,2.2-Introduction. No clinical evidence of rejection of the product has been observed after application to acute or chronic wounds. Because they do not contain antigen-presenting cells, cultured allogeneic keratinocytes were initially expected to serve as a permanent skin substitute. However, despite the absence of clinical rejection to date, there is no evidence of long-term persistence of the product at the treatment site. It has been suggested that Apligraf, and GINTUIT, acts as a "smart" material for wound healing by interacting with the surrounding environment to promote healing. It provides components with multiple actions, interacts with wounds in biological and physical ways, and appears to adapt to the wound environment, and probably produces numerous prohealing cytokines. These include interleukin 1, interleukin 3, interleukin 6, interleukin 8, transforming growth factor alpha and beta, granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor and basic fibroblast growth factor. (BLA STN 125400)

Comparing the Indicated Use of GINTUIT versus Apligraf

GINTUIT is manufactured using the same process as Apligraf, and is designed to be applied over a surgically created vascular wound in oral mucosal gingival tissue. As proposed in the BLA supplement, the prescribing information for GINTUIT will be specific to the new oral indication, and GINTUIT will be presented in a different shipping container than the original Apligraf. Both products are intended to be applied topically to a well-defined, surgically prepared wound or tissue defect prior to application of the product. Both products are placed directly in contact with the soft tissue wound, extending beyond the wound margins. The healing of both oral mucosal and cutaneous tissues is expected to proceed through similar and consistent physiological stages.

However, there are several important differences. GINTUIT is intended to treat acute wounds, whereas Apligraf is indicated for the treatment of chronic wounds, which are known to be more difficult to manage. In addition, the larger standard Apligraf membrane is generally folded into a smaller geometry during clinical application. The function of the viable cells as part of the final product is not known, and their role in wound healing in the oral mucosa has not been elucidated. While the mechanism of action is not fully understood, it is likely complex and multi-modal, involving the keratinocytes, fibroblasts, collagen/extracellular matrix, and growth factors/cytokines produced by the cells.

Clinical Trial Data in Support of GINTUIT

Following the initial FDA approval of Apligraf for the treatment of venous leg ulcers (1998) and diabetic foot ulcers (June 2000), GINTUIT is now being reviewed by the Office of Cellular, Tissue and Gene Therapies. In support of this application, the sponsor has submitted data from three clinical trials. Data for safety and efficacy, and background information was reviewed by an advisory committee on November 17, 2011. The clinical trials and the results of the advisory committee meeting are reviewed below. The original name as submitted in the BLA was "Apligraf (oral)".

1. Pilot Study 05-PER-001-CTX

A pilot clinical trial to assess the safety and efficacy of Apligraf(oral) in establishing a functional zone of attached gingiva. This was a prospective, randomized, single center, pilot study (n=25) in which subjects served as their own controls (with matching for teeth and gingival condition). The safety of Apligraf was assessed by spontaneous adverse event reporting and by clinical assessment to detect local and systemic reactions. No deaths or other severe adverse events were reported, and investigators did not consider any adverse events to be related to the study treatment. There were no wound infections, allergic reactions, or signs of local or systemic reactions. Adverse events included four cases of sinusitis, one upper respiratory infection, one migraine headache, and several miscellaneous, unrelated adverse events, including one case of post-menopausal bleeding and one case of mastitis. PCR studies at six months showed no sign of Apligraf DNA persistence in the patients' graft sites.

OBE Assessment: Clinical trial data submitted in support of the BLA for Apligraf(oral) do not reveal any major safety concern.

2. Pivotal Study 06-PER-002-CTX

A clinical trial to evaluate CelTx (Apligraf (oral)) as an alternative to tissue from the palate to enhance oral soft tissue regeneration and wound healing

This study included 96 subjects. Three serious adverse events (SAEs) were reported during the study and all three events were assessed by the investigator to be either not related (pneumonia and chest pain) or of unlikely relationship (metastatic malignant fibrous histiocytoma; mass was recognized prior to the study treatment). An additional non-oral cavity malignancy of follicular thyroid carcinoma was reported during the study, which in the assessment of the Investigator was not related. Two non-serious AEs (gingival injury and gingival pain) were assessed as possibly or probably related, respectively. In both cases, the product had been placed incorrectly. DNA persistence testing of the pilot study 6-Month biopsy samples did not detect the presence of Apligraf (oral) at the surgical site.

OBE Assessment: Clinical trial data submitted in support of the BLA for Apligraf(oral) do not reveal any major safety concern.

3. Study 07-PER-004-CTX (submerged)

A prospective, randomized, controlled pilot study of CelTx (Apligraf) as an alternative to tissue from the palate in the treatment of gingival recession requiring root coverage
This was a prospective, randomized, controlled, single-center, pilot study (n=15). This study was terminated early upon mutual agreement between the sponsor and the principal investigator due to suboptimal clinical outcomes. Over the course of study conduct, there were two study design changes (ie, ----b(4)----------) that resulted in three distinct groups of subjects. The differences between these subject groups were so great that data could not be combined and analyzed for effectiveness. The data is included in the safety database.

OBE Assessment: This study was terminated early upon mutual agreement between the sponsor and the principal investigator, therefore can not be adequately evaluated.

4. **Advisory Committee Recommendations**

Advisory Committee met on Nov. 17, 2011. Generally, the committee agreed that the data does not suggest major safety concerns. Some members felt that the product, if licensed, would be used in children, and suggested clinical trials with safety follow-up of at least 6 months. This triggered a PREA Post-Marketing Requirement. There was no Safety Post-Marketing Requirement requested.
For more detailed information concerning this session, presentations and committee discussions, please refer to the meeting transcripts available on the FDA website at:

http://www.fda.gov/AdvisoryCommittee/CommitteesMeetingMaterials/Blood/VaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/default.htm

Postmarketing Experience with Apligraf

From the sponsor, the overall Apligraf US postmarketing safety experience from 22 May 1998 to 31 December 2010 included a total of 197 adverse events reported to Organogenesis for the two previously approved indications. There were six serious adverse events: infection (2 reports), allergic reactions (2), erosion (1), and squamous cell carcinoma (1). The report of squamous cell carcinoma (SCC) was at the graft site, but thought to be pre-existing, as the patient had previous SCC excised from scalp and multiple pre-cancerous skin lesions noted in the region.

CDRH's safety database (MDR/Maude) contains post-marketing safety data for Apligraf for the two approved indications: venous leg ulcer and diabetic foot ulcer. Through 30 June 2011, 11 adverse events have been reported to MAUDE: injuries (8 reports), malfunctions (2), and other (1). Within the results of this analysis, one report described an off-label use: Apligraf was placed in an abdominal wound after major abdominal surgery and non-healing. The adverse event of cellulitis reported. No reports mentioned off-label use in any type of dental application.

OBE Safety Assessment

21 CFR 601.25 (d)(1) states that safety of a licensed biological product means relative freedom from harmful effect to the persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition for the recipient at the time. Proof of safety shall consist of adequate tests by methods applicable to show that the biological product is safe for the prescribed conditions of use.

Assessment of safety is based on postmarketing reports for Apligraf and clinical trials for Apligraf (oral). Of the total patients treated with Apligraf in completed clinical trials to 31 December 2010, 19 (1.2%) were reported to have developed a malignancy or recurrence of a malignancy after application of Apligraf. Five of these patients had been treated with Apligraf on a skin cancer excision site, and four had cancers known to be present at the time of application. The time between Apligraf application and the diagnosis of a malignancy was generally less than a year, and there was no specific pattern in the type of cancer that developed. There were two cases of melanoma. One occurred in a patient immunosuppressed for kidney transplantation, and one was a case of intracerebral melanoma after Apligraf was placed at the site of excision of a primary scalp melanoma. These were not considered to be related to the use of the product by the investigator.

It is not known whether the safety information obtained for diabetic foot ulcer and venous leg ulcer can be extrapolated to the product's use in oral procedures. New or recurrent malignancies have been reported after Apligraf; a causal relationship with the product has not been established.

Pharmacovigilance Planning Assessment Criteria

When a new product is marketed, the exposed population may differ from the population studied in pre-approval trials. For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) is sufficient for post-marketing risk assessment. As outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (http://fda.gov/CDER/guidance/63590CC.htm), FDA believes pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

Major Safety Concerns

- Important Identified Risks: None

- Important Potential Risks: Gingival Injury and Gingival Pain

    - Misplacement of Apligraf (oral) resulted in two adverse events, gingival injury and gingival pain, in **Study 06-PER-002-CTX.** These events occurred only in the training subjects and not in the efficacy cohort. These risks have been addressed in the package insert (Section 6 - Adverse Reactions).

- Important Missing Information: The safety of Apligraf (oral) has not been established in pregnant or lactating women. The safety of Apligraf (oral) has not been established in children or adolescents.

    - Karyology testing for related commercially available products has shown that chromosomal aberrations can occur. Theoretically, karyotype instability could occur and might affect the product's safety and efficacy, although no karyotype instability has been noted thus far. There have been no documented clinical or histological

reports of tumor formation at the site of application of Apligraf (oral). **There have been no reports of oropharyngeal malignancies related to use of the product.**

- However, because of this theoretical risk, DE recommends asking the sponsor for expedited (15-day) reporting of malignancies (at both the graft site and remote locations) for the first year after licensure.

Routine Plans

Routine pharmacovigilance activities will be conducted by Organogenesis Regulatory Affairs and Medical Affairs Departments under standard operating procedures to determine the frequency, causality, relationship, and severity of adverse events. The Regulatory Affairs Department is responsible for adherence to the applicable pharmacovigilance standard operating procedures (SOPs) and managing the collection and submission of expedited and periodic safety update reports of all suspected adverse events reported to Organogenesis. Organogenesis will be the sole distributor of GINTUIT; therefore no other parties are expected to receive adverse event reports for this product. The Medical Affairs Department will review postmarketing safety data from all sources to detect and evaluate changes suggestive of new safety signals. Organogenesis will oversee an outside pharmacovigilance contract organization (PVCO) in generating individual case safety reports for each adverse event in accordance with ICH E2B, maintaining the GINTUIT pharmacovigilance database, and compiling Periodic Safety Update Reports. Safety signals will be reviewed to determine if further action is required. Any GINTUIT lot-related safety finding will be addressed in a multi-functional team review consisting, but not limited to, Regulatory, Medical Affairs and Quality Assurance.

Non-Routine Plans

- Organogenesis does not have any ongoing GINTUIT clinical studies.
- Organogenesis has agreed to submit a protocol for **Clinical Study Protocol 12-PER-007-LCC**, to evaluate safety and efficacy in adolescent patients, as a post-marketing requirement. The final draft protocol will be submitted and reviewed by OCTGT. Adverse events will be submitted as part of the IND.

OBE Assessment and Recommendations

- The sponsor has submitted a detailed pharmacovigilance plan in according with the ICH E2E PVP guidance (http://fda.gov/CDER/guidance/63590CC.htm). The Pharmacovigilance Plan for the product GINTUIT is acceptable. When used for the approved indications, the adverse event profile appears to be acceptable.
- DE agrees with a Phase III PREA-required postmarketing study to evaluate safety and efficacy for use in adolescents. A draft protocol has been submitted will be reviewed by OCTGT.
- There have been no documented clinical or histological reports of tumor formation at the site of application of Apligraf (oral). DE recommends asking the sponsor for expedited (15-day) reporting of malignancies (at both the graft site and remote locations) for the first year after licensure.

Letter Ready Comments

- DE agrees with OCTGT's request for a post-marketing study for use in pediatric age group. OCTGT will draft the PMR details in conjunction with the sponsor. This is consistent with the Advisory Committee opinions.
- A study, **Clinical Study Protocol 12-PER-007-LCC,** to evaluate the safety and efficacy in adolescents (ages 12-18) has been agreed to by Organogenesis, as a PREA post-marketing requirement. Details of the protocol will be finalized by Organogenesis and the Office of Cellular, Tissue and Gene Therapies within the Center for Biologics Evaluation and Research of the Food and Drug Administration (OCTGT).
- The study will be initiated under an Investigational New Drug application.
- Results from **Clinical Study Protocol 12-PER-007-LCC** should be submitted in the IND to OCTGT.
- DE recommends asking the sponsor for expedited (15-day) reporting of malignancies (at both the graft site and remote locations) for the first year after licensure.