CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: December 20, 2012

To: NDA 203441

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review and Concurrence of ONDQA recommendation for NDA 203441, Gattex® teduglutide, for injection, 5 mg per vial (10 mg/mL after reconstituted). Teduglutide is a new molecular entity (NME).

Teduglutide in NDA 203441 is proposed for the treatment of adult patients with short bowel syndrome (SBS) and improvement of intestinal absorption of fluid and nutrients.

I have assessed the ONDQA reviews of NDA 203441 by Yichun Sun, Ph.D. and concur with the ONDQA recommendation of Approval. The initial ONDQA CMC review was entered into DARRTS on July 27, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites, pending labeling issues and pending results for the methods validation consult. A methods validation consult was sent to the Division of Pharmaceutical Analysis (DPA), Office of Testing and Research. According to the Method Validation Report Summary entered into DARRTS by Michael Trehy, Ph.D. on November 21, 2012 the two HPLC methods were determined to be acceptable for quality control and regulatory purposes by Kallol Biswas, Ph.D. An ONDQA Biopharmaceutics review was not preformed due to the proposed dosage form. On December 14, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES after the applicant withdrew the [redacted] (b) (4) drug substance manufacturing site from the application. A second CMC review was entered into DARRTS on December 14, 2012 updating the status of the recommendation from the Office of Compliance, resolution of labeling issues and acceptability of the methods.

Teduglutide for injection is supplied in a sterile, single-use 3-mL, USP Type I glass vial containing 5 mg of teduglutide as a white lyophilized powder in a 30-vial kit and a single-vial kit. The lyophilized powder is intended to be reconstituted with 0.5 mL of sterile Water for Injection (sWFI), USP, immediately before administration by subcutaneous injection. Each vial of teduglutide also contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, and 3.434 mg dibasic sodium phosphate heptahydrate. The sWFI is provided in a prefilled syringe. The product should be used within 3 hrs after reconstitution.

The drug substance, teduglutide is manufactured by [redacted] (b) (4) . A [redacted] (b) (4) month retest date is recommended when the drug substance is stored at -20° ± 5°C or below.

The drug product, teduglutide for injection, is manufactured by Hospira, Inc, McPherson, KS. The Sterile Water for Injection (sWFI) prefilled syringes are manufactured by (b) (4) The teduglutide and sWFI are co-packaged at (b) (4)

A 36 months expiration dating period for the product stored refrigerated at 2°C to 8°C (36°F and 46°F), prior to dispensing. Once dispensed to the patient the product may be stored at room temperature up to 25°C (77°F) (b) (4).

The drug product is packaged in two configurations, a single-vial kit and a 30-vial kit. The single vial kit comes as one package (single box) with the non-drug components included in the box. The 30-vial kit comes as two packages, one for the drug product vials and another for the non-drug components. The box containing the non-drug components is stored at room temperature. The box containing the drug product vials must be stored refrigerated until dispensed. The packaging configuration then requires the dispensing pharmacist to remove the drug vials from their outer container, add the drug vials to the larger box containing the non-drug components, add a use by date to the outer carton and then dispense the whole kit which will be stored at room temperature by the patient (b) (4)

The kits are as described below:
The product to be dispensed either a single-vial kit or a 30-vial kit. The single-vial kit is pre-assembled and ready to be used. It contains:

One-vial kit (NDC 68875-0101-4):

- One single-use vial of drug
- One disposable prefilled syringe containing 0.5 mL Sterile Water for Injection USP for reconstitution, with a separate needle (22G x 1½ in) to attach to the syringe
- One sterile disposable 1-mL syringe with needle (26G x 5/8 in) for dosing
- Four alcohol swabs

The 30-vial kit is to be assembled by a pharmacist with the following two cartons:

Carton of Drug (NDC 68875-0101-2):

- Thirty single-use vials of drug

Carton of Ancillary Supplies (NDC 68875-0101-3):

- Thirty disposable prefilled syringes containing 0.5 mL Sterile Water for Injection Thirty separate needles (22G x 1½ in) to attach to the syringes for reconstitution
- Thirty sterile disposable 1-mL syringes with needle (26G x 5/8 in)
- Sixty alcohol swabs

Reconstitution of the lyophilized drug with 0.5 mL of preservative-free Sterile Water for Injection, provided in a prefilled syringe, is required prior to subcutaneous administration of the drug. Reconstituted GATTEX is a sterile, clear, colorless to light straw-colored 10 mg/mL solution, which is essentially free from particulates. Upon reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe, a maximum of 0.38 mL of the reconstituted solution which contains 3.8 mg of teduglutide can be withdrawn from the vial for dosing.

The container carton labels for the two packaging configurations are not well designed. Valuable information is contained on the sides and bottom panels instead of the front (top) panel. Messages to the pharmacist related to storage and dispensing are not readily visible. Nor are instructions completely clear. For example, there is a place on the front label for the pharmacist to apply a (b) (4). However, these issues do not affect the approval decision for this application.

During the writing of this review it was also noted that the drug vials contained incorrect storage conditions. (b) (4) This was initially justified by stating that having multiple storage conditions on the label may confuse the patient and that the patient was the person most likely to see the individual vials (due to them being packaged in a kit). After a discussion with relevant members of the review team, it was determined that the vials should be labeled according to the requirements for long term stability. The Applicant was contacted on December 19, 2012 to inform them of this necessary change and also to request that the front panels contain a storage condition statement directed to the patient. The vial label was updated to state "Prior to dispensing, store at 2°C to 8°C (36°F to 46°F). Do not freeze" on December 20, 2012. The following statement will be added to the outer cartons front panel: "Attention patients: Store at room temperature up to 25°C (77°F). Do not freeze." Section 16 HOW SUPPLIED/STORAGE AND HANDLING of the package insert will be revised to be consistent with the outer cartons.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

There is one ONDQA related Post Marketing Commitment (PMC). The PMC calls for: "Elemental Impurities specifications will be expanded to include limits and testing for all metals, as recommended in USP <232>." This is to be implemented by the Applicant by March 31, 2013.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

The secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

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/s/

TERRANCE W OCHELTREE
12/20/2012

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