CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203752Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
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Date: October 12, 2012

To: Caroline Strasinger, Review Chemist, ONDQA

Through: Benjamin Westenberger, Deputy Director, Division of Pharmaceutical Analysis

From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis

Subject: Crystal formation of [redacted] (b) (4) Estradiol TDDS with elevated humidity

Objective:
To determine if crystals form when the [redacted] (b) (4) estradiol transdermal drug delivery system is exposed to elevated humidity.

Background:
ONDQA Review Chemist, Dr. Caroline Strasinger, submitted a Methods Validation Request for NDA 203-752, Noven Pharmaceuticals's [redacted] (b) (4) (Estradiol Transdermal System). The requested determinations were for Release Liner Peel Force, Shear Adhesion, Peel Adhesion, Probe Tack, and Cold Flow. Additionally, Dr. Strasinger requested that samples (opened and with adhesive matrix exposed) be placed in a humid environment for 2-5 days and examined for crystals using a microscope.

Conclusions:
No crystals were observed for the ambient Day 1- Day 4 samples with their release liners on and off. No crystals were observed for the chamber (32°C and 75% RH) Day 1- Day 4 samples with their release liners on and off. Also, no crystals were observed for the chamber Day 1 - Day 4 samples that were in their intact pouches before opening.

Samples/Materials:
NDA samples of 6.6 cm^2, 3.3 cm^2, 2.475 cm^2, and [redacted] (b) (4) [redacted] (b) (4) estradiol transdermal systems. (See Attachment A.)

Experimental/Methods:
For each dosage, systems removed from their pouches with their release liners intact, systems removed from their pouches with their release liners removed, and systems in their intact (sealed) pouches were placed in an environmental test chamber at 32°C and 75% relative humidity for 4 days. Also, systems in their intact (sealed) pouches were placed on the lab bench at ambient conditions.

Each test day, the designated samples were removed from the chamber as well as the designated ambient samples and examined for crystals macroscopically and microscopically. (See Attachment A.) After examination, the samples were returned to their storage conditions.

Results/Discussion:
Ambient conditions ranged from 17°C-22°C and 42%-66% relative humidity (RH), and the environmental test chamber was set to 32°C and 75% RH. No crystals were observed for the ambient Time 0, Day 1, Day 2, Day 3, and Day 4 samples with their release liners on and off. No crystals were observed for the chamber Day 1, Day 2, Day 3, and Day 4 samples with their release liners on and off. No crystals were observed for the chamber Day 1, Day 2, Day 3, and Day 4 samples that were in their intact pouches before opening. For the samples that had their release liners off, some dirt/threads from the air adhered to the adhesive. (See Attachment B.)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL L TREHY
10/11/2012

NDA 203752
ADDENDUM

Minivelle (estradiol transdermal system)

Noven Pharmaceuticals Inc.

Caroline Strasinger, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC Review of NDA 203752
For the Division of Reproductive and Urological Products

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