CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207631

Name: Nilutamide Tablets, 150 mg

Sponsor: ANI Pharmaceuticals Inc.

Approval Date: July 15, 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207631

APPROVAL

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Director, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Nilutamide Tablets, 150 mg.

Reference is also made to your amendments dated September 25, 2014 (both amendments); May 28 and November 11, 2015; and January 25 and March 18, 2016.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the **ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Nilutamide Tablets, 150 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Nilandron Tablets 150 mg, of Concordia Pharmaceuticals Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

Post marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Carol Holquist

Digitally signed by Carol Holquist
Date: 7/15/2016 04:19:45PM
GUID: 508da712000293e0f6d8acfd3c5e67fe

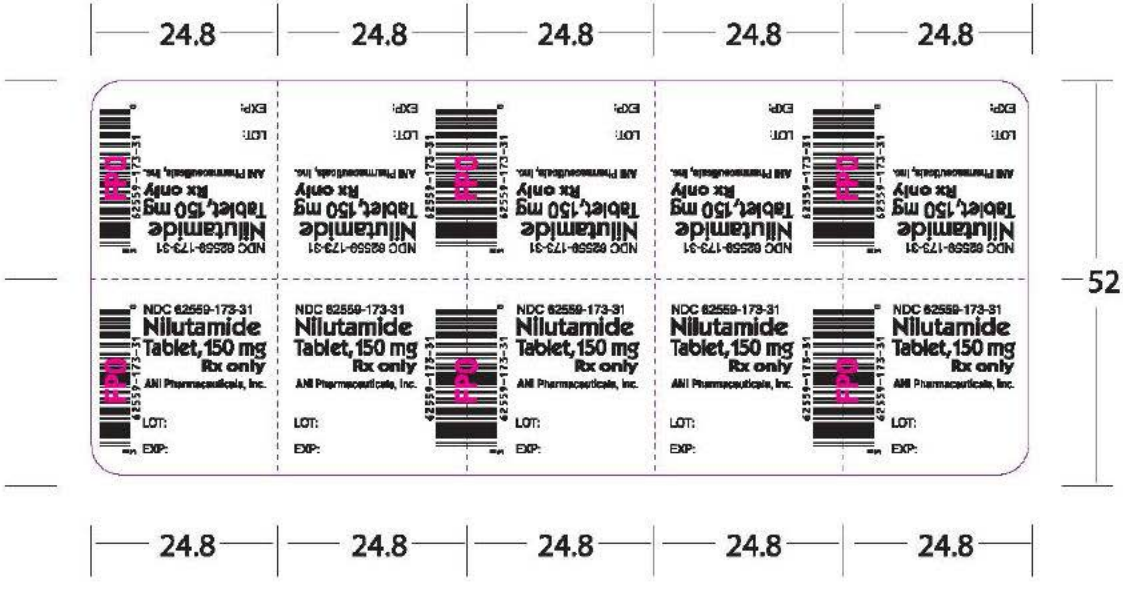
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

LABELING

11/06/15


24.8
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52
NDC 62559-173-31
Nilutamide
Tablet, 150 mg
Rx only
ANI Pharmaceuticals, Inc.
LOT:
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5

Nilutamide Tablets 150 mg Rx only

NDC 62559-173-31

LOT:

EXP:

Unvarnished area

NDC 62559-173-31

Nilutamide Tablets

150 mg

Rx only

ani Pharmaceuticals, Inc.

30 (3 x 10) Unit-of-Use Tablets

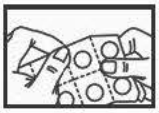
NDC 62559-173-31

Nilutamide Tablets

150 mg

Rx only

The blisters in this package are child-resistant.



To remove, tear off tablet.

Peel paper at corner and remove.

Push tablet through foil.

Nilutamide Tablets 150 mg Rx only

Each tablet contains: Nilutamide .....150 mg

Usual Dosage: 300 mg once daily for 30 days, followed thereafter by 150 mg once daily. See package insert for full prescribing information.

WARNING: Keep out of reach of children.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]

Protect from light.

Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623
9514 Rev 12/15

7/8

2 1/8

6 19/32

11/06/15

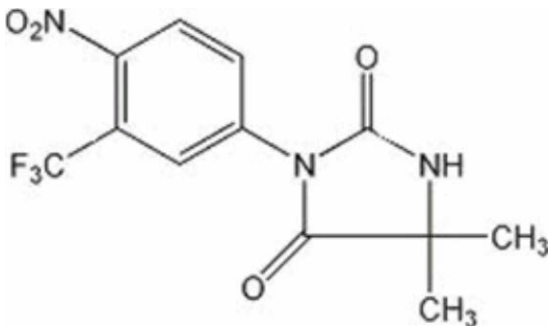
(b) (4)

Nilutamide Tablets

Rx Only 9625 Rev 12/15

DESCRIPTION

Nilutamide Tablets contain nilutamide, a nonsteroidal, orally active antiandrogen having the chemical name 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione with the following structural formula:



Nilutamide is a microcrystalline, white to practically white powder with a molecular weight of 317.25.

Its molecular formula is $C_{12}H_{10}F_3N_3O_4$.

It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [<0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

Each Nilutamide Tablet contains 150 mg of nilutamide. The inactive ingredients in Nilutamide Tablets include: calcium stearate, docusate sodium, lactose, povidone, corn starch, and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action

Prostate cancer is known to be androgen sensitive and responds to androgen ablation. In animal studies, nilutamide has demonstrated antiandrogenic activity without other hormonal (estrogen, progesterone, mineralocorticoid, and glucocorticoid) effects. *In vitro*, nilutamide blocks the effects of testosterone at the androgen receptor level. *In vivo*, nilutamide interacts with the androgen receptor and prevents the normal androgenic response.

Pharmacokinetics

Absorption

Analysis of blood, urine, and feces samples following a single oral 150-mg dose of [^{14}C]-nilutamide in patients with metastatic prostate cancer showed that the drug is rapidly and completely absorbed and that it yields high and persistent plasma concentrations.

Distribution
After absorption of the drug, there is a detectable distribution phase. There is moderate binding of the drug to plasma proteins and low binding to erythrocytes. The binding is nonsaturable except in the case of alpha-1-glycoprotein, which makes a minor contribution to the total concentration of proteins in the plasma. The results of binding studies do not indicate any effects that would cause nonlinear pharmacokinetics.

Metabolism
The results of a human metabolism study using ^{14}C-radiolabelled tablets show that nilutamide is extensively metabolized and less than 2% of the drug is excreted unchanged in urine after 5 days. Five metabolites have been isolated from human urine. Two metabolites display an asymmetric center, due to oxidation of a methyl group, resulting in the formation of D- and L-isomers. One of the metabolites was shown, *in vitro*, to possess 25 to 50% of the pharmacological activity of the parent drug, and the D-isomer of the active metabolite showed equal or greater potency compared to the L-isomer. However, the pharmacokinetics and the pharmacodynamics of the metabolites have not been fully investigated.

Elimination
The majority (62%) of orally administered [^{14}C]-nilutamide is eliminated in the urine during the first 120 hours after a single 150-mg dose. Fecal elimination is negligible, ranging from 1.4% to 7% of the dose after 4 to 5 days. Excretion of radioactivity in urine likely continues beyond 5 days. The mean elimination half-life of nilutamide determined in studies in which subjects received a single dose of 100 to 300 mg ranged from 38.0 to 59.1 hours with most values between 41 and 49 hours. The elimination of at least one metabolite is generally longer than that of unchanged nilutamide (59 to 126 hours). During multiple dosing of 150 mg nilutamide (given as 3 × 50 mg) twice a day, steady state was reached within 2 to 4 weeks for most patients, and mean steady state AUC_{0-12} was 110% higher than the $AUC_{0-\infty}$ obtained from the first 150 mg dose. These data and *in vitro* metabolism data suggest that, upon multiple dosing, metabolic enzyme inhibition may occur for this drug.

Clinical Studies
Nilutamide through its antiandrogenic activity can complement surgical castration, which suppresses only testicular androgens. The effects of the combined therapy were studied in patients with previously untreated metastatic prostate cancer.

In a double-blind, randomized, multicenter study that enrolled 457 patients (225 treated with orchiectomy and Nilutamide Tablets, 232 treated with orchiectomy and placebo), the Nilutamide Tablets group showed a statistically significant benefit in time to progression and time to death. The results are summarized below.

	NILUTAMIDE TABLETS	PLACEBO

Median Survival (months)	27.3	23.6
Progression-Free Survival (months)	21.1	14.9
Complete or Partial Regression	41%	24%
Improvement in Bone Pain	54%	37%

INDICATIONS AND USAGE

Metastatic Prostate Cancer
Nilutamide Tablets are indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

For maximum benefit, treatment with Nilutamide Tablets must begin on the same day as or on the day after surgical castration.

CONTRAINDICATIONS
Nilutamide Tablets are contraindicated:
- in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment)
- in patients with severe respiratory insufficiency
- in patients with hypersensitivity to nilutamide or any component of this preparation.

WARNINGS

Interstitial Pneumonitis

Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. A small study in Japanese subjects showed that 8 of 47 patients (17%) developed interstitial pneumonitis. Reports of interstitial changes including pulmonary fibrosis that led to hospitalization and death have been reported rarely post-marketing. Symptoms included exertional dyspnea, cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitial changes, and pulmonary function tests revealed a restrictive pattern with decreased DLco. Most cases occurred within the first 3 months of treatment with Nilutamide Tablets, and most reversed with discontinuation of therapy. A routine chest X-ray should be performed prior to initiating treatment with Nilutamide Tablets. Baseline pulmonary function tests may be considered. Patients should be instructed to report any new or worsening shortness of breath that they experience while on Nilutamide Tablets. **If symptoms occur, Nilutamide Tablets should be immediately discontinued until it can be determined if the symptoms are drug related.**

Hepatitis

Rare cases of death or hospitalization due to severe liver injury have been reported post-marketing in association with the use of Nilutamide Tablets. Hepatotoxicity in these reports generally occurred within the first 3 to 4 months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in 1% of Nilutamide Tablet patients in controlled clinical trials. Serum transaminase levels should be measured prior to starting treatment with Nilutamide Tablets, at regular intervals for the first 4 months of treatment, and periodically thereafter. Liver function tests should also be obtained at the first sign or symptom suggestive of liver dysfunction, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, Nilutamide Tablets should be immediately discontinued with close follow-up of liver function tests until resolution.

Use in Women
Nilutamide Tablets have no indication for women, and should not be used in this population, particularly for non-serious or non-life threatening conditions.

Other
Foreign post-marketing surveillance has revealed isolated cases of aplastic anemia in which a causal relationship with Nilutamide Tablets could not be ascertained.

PRECAUTIONS

General
Antiandrogen Withdrawal Syndrome
Patients whose disease progresses while being treated with an antiandrogen may experience clinical improvement with discontinuation of the antiandrogen.

Information for Patients
Patients should be informed that Nilutamide Tablets should be started on the day of, or on the day after, surgical castration. They should also be informed that they should not interrupt their dosing of Nilutamide Tablets or stop taking this medication without consulting their physician.

Because of the possibility of interstitial pneumonitis, patients should also be told to report immediately any dyspnea or aggravation of pre-existing dyspnea.

Because of the possibility of hepatitis, patients should be told to consult with their physician should nausea, vomiting, abdominal pain, or jaundice occur.

Because of the possibility of an intolerance to alcohol (facial flushes, malaise, hypotension) following ingestion of Nilutamide Tablets, it is recommended that intake of alcoholic beverages be avoided by patients who experience this reaction. This effect has been reported in about 5% of patients treated with Nilutamide Tablets.

In clinical trials, 13% to 57% of patients receiving Nilutamide Tablets reported a delay in adaptation to dark, ranging from seconds to a few minutes, when passing from a lighted

area to a dark area. This effect sometimes does not abate as drug treatment is continued. Patients who experience this effect should be cautioned about driving at night or through tunnels. This effect can be alleviated by the wearing of tinted glasses.

Drug Interactions
In vitro, nilutamide has been shown to inhibit the activity of liver cytochrome P-450 isoenzymes and, therefore, may reduce the metabolism of compounds requiring these systems.

Consequently, drugs with a low therapeutic margin, such as vitamin K antagonists, phenytoin, and theophylline, could have a delayed elimination and increases in their serum half-life leading to a toxic level. The dosage of these drugs or others with a similar metabolism may need to be modified if they are administered concomitantly with nilutamide. For example, when vitamin K antagonists are administered concomitantly with nilutamide, prothrombin time should be carefully monitored and, if necessary, the dosage of vitamin K antagonists should be reduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Administration of nilutamide to rats for 18 months at doses of 0, 5, 15, or 45 mg/kg/day produced benign Leydig cell tumors in 35% of the high-dose male rats (AUC exposures in high-dose rats were approximately 1 to 2 times human AUC exposures with therapeutic doses). The increased incidence of Leydig cell tumors is secondary to elevated luteinizing hormone (LH) concentrations resulting from loss of feedback inhibition at the pituitary. Elevated LH and testosterone concentrations are not observed in castrated men receiving Nilutamide Tablets. Nilutamide had no effect on the incidence, size, or time of onset of any spontaneous tumor in rats.

Nilutamide displayed no mutagenic effects in a variety of *in vitro* and *in vivo* tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests).

In reproduction studies in rats, nilutamide had no effect on the reproductive function of males and females, and no lethal, teratogenic, or growth-suppressive effects on fetuses were found. The maximal dose at which nilutamide did not affect reproductive function in either sex or have an effect on fetuses was estimated to be 45 mg/kg orally (AUC exposures in rats approximately 1 to 2 times human therapeutic AUC exposures).

Pregnancy
Pregnancy Category C; Animal reproduction studies have not been conducted with nilutamide. It is also not known whether nilutamide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Nilutamide should be given to a pregnant woman only if clearly needed.

Pediatric Use
Safety and effectiveness in pediatric patients have not been determined.

Animal Pharmacology and Toxicology
Administration of Nilutamide Tablets to beagle dogs resulted in drug-related deaths at dose levels that produce AUC exposures in dogs much lower than the AUC exposures of men

receiving the therapeutic doses of 150 and 300 mg/day. Nilutamide-induced toxicity in dogs was cumulative with progressively lower doses producing death when given for longer durations. Nilutamide given to dogs at 60 mg/kg/day (1 to 2 times human AUC exposure) for 1 month produced 100% mortality. Administration of 20 and 30 mg/kg/day nilutamide (1/2 to 1 times human AUC exposure) for 6 months resulted in 20% and 70% mortality in treated dogs. Administration to dogs of 3, 6, and 12 mg/kg/day nilutamide (1/10 to 1/2 human AUC exposure) for 1 year resulted in 8%, 33%, and 50% mortality, respectively. **A "no-effect level" for nilutamide-induced mortality in dogs was not identified.** Pathology data from the one-year oral toxicity study suggest that the deaths in dogs were secondary to liver toxicity. Marked-to-massive hepatocellular swelling and vacuolization were observed in affected dogs. Liver toxicity in dogs was not consistently associated with elevations of liver enzymes.

Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1 to 2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis).

The hepatic and pulmonary adverse effects observed in nilutamide-treated animals and men are similar to effects observed with another nitroaromatic compound, nitrofurantoin. Nilutamide and nitrofurantoin are both metabolized *in vitro* to nitroanion free-radicals by microsomal NADPH-cytochrome P450 reductase in the lungs and liver of rats and humans.

ADVERSE REACTIONS

The following adverse experiences were reported during a multicenter clinical trial comparing Nilutamide Tablets + surgical castration versus placebo + surgical castration. The most frequently reported (greater than 5%) adverse experiences during treatment with Nilutamide Tablets in combination with surgical castration are listed below. For comparison, adverse experiences seen with surgical castration and placebo are also listed.

Adverse Experience	Nilutamide Tablets + surgical castration (N=225) % All	Placebo + surgical castration (N=232) % All
Cardiovascular System		
Hypertension	5.3	2.6
Digestive System		
Nausea	9.8	6.0
Constipation	7.1	3.9
Endocrine System		
Hot flushes	28.4	22.4
Metabolic and Nutritional System		
Increased AST	8.0	3.9
Increased ALT	7.6	4.3
Nervous System		
Dizziness	7.1	3.4

Respiratory System		
Dyspnea	6.2	7.3
Special Senses		
Impaired adaptation to dark	12.9	1.3
Abnormal vision	6.7	1.7
Urogenital System		
Urinary tract infection	8.0	9.1

The overall incidence of adverse experiences was 86% (194/225) for the Nilutamide Tablets group and 81% (188/232) for the placebo group.

The following adverse experiences were reported during a multicenter clinical trial comparing Nilutamide Tablets + leuprolide versus placebo + leuprolide. The most frequently reported (greater than 5%) adverse experiences during treatment with Nilutamide Tablets in combination with leuprolide are listed below. For comparison, adverse experiences seen with leuprolide and placebo are also listed.

Adverse Experience	Nilutamide Tablets + leuprolide (N=209) % All	Placebo + leuprolide (N=202) % All
Body as a Whole		
Pain	26.8	27.7
Headache	13.9	10.4
Asthenia	19.1	20.8
Back pain	11.5	16.8
Abdominal pain	10.0	5.4
Chest pain	7.2	4.5
Flu syndrome	7.2	3.0
Fever	5.3	6.4
Cardiovascular System		
Hypertension	9.1	9.9
Digestive System		
Nausea	23.9	8.4
Constipation	19.6	16.8
Anorexia	11.0	6.4
Dyspepsia	6.7	4.5
Vomiting	5.7	4.0
Endocrine System		
Hot flushes	66.5	59.4
Impotence	11.0	12.9
Libido decreased	11.0	4.5
Hemic and Lymphatic System		
Anemia	7.2	6.4

Metabolic and Nutritional System		
Increased AST	12.9	13.9
Peripheral edema	12.4	17.3
Increased ALT	9.1	8.9
Musculoskeletal System		
Bone Pain	6.2	5.0
Nervous System		
Insomnia	16.3	15.8
Dizziness	10.0	11.4
Depression	8.6	7.4
Hypesthesia	5.3	2.0
Respiratory System		
Dyspnea	10.5	7.4
Upper respiratory infection	8.1	10.9
Pneumonia	5.3	3.5
Skin and Appendages		
Sweating	6.2	3.0
Body hair loss	5.7	0.5
Dry skin	5.3	2.5
Rash	5.3	4.0
Special Senses		
Impaired adaptation to dark	56.9	5.4
Chromatopsia	8.6	0.0
Impaired adaptation to light	7.7	1.0
Abnormal vision	6.2	4.5
Urogenital System		
Testicular atrophy	16.3	12.4
Gynecomastia	10.5	11.9
Urinary tract infection	8.6	21.3
Hematuria	8.1	7.9
Urinary tract disorder	7.2	10.4
Nocturia	6.7	6.4

The overall incidence of adverse experiences is 99.5% (208/209) for the Nilutamide Tablets group and 98.5% (199/202) for the placebo group.

Some frequently occurring adverse experiences, for example hot flushes, impotence, and decreased libido, are known to be associated with low serum androgen levels and known to occur with medical or surgical castration alone. Notable was the higher incidence of visual disturbances (variously described as impaired adaptation to darkness, abnormal vision, and colored vision), which led to treatment discontinuation in 1% to 2% of patients.

Interstitial pneumonitis occurred in one (<1%) patient receiving Nilutamide Tablets in combination with surgical castration and in seven patients (3%) receiving Nilutamide Tablets in combination with leuprolide and one patient receiving placebo in combination with leuprolide.

Overall, it has been reported in 2% of patients receiving Nilutamide Tablets. This included a report of interstitial pneumonitis in 8 of 47 patients (17%) in a small study performed in Japan.

In addition, the following adverse experiences were reported in 2 to 5% of patients treated with Nilutamide Tablets in combination with leuprolide or orchiectomy.

Body as a Whole:
- Malaise (2%)

Cardiovascular System:
- Angina (2%)
- Heart Failure (3%)
- Syncope (2%)

Digestive System:
- Diarrhea (2%)
- Gastrointestinal Disorder (2%)
- Gastrointestinal Hemorrhage (2%)
- Melena (2%)

Metabolic and Nutritional System:
- Alcohol Intolerance (5%)
- Edema (2%)
- Weight Loss (2%)

Musculoskeletal System:
- Arthritis (2%)

Nervous System:
- Dry Mouth (2%)
- Nervousness (2%)
- Paresthesia (3%)

Respiratory System:
- Cough Increased (2%)
- Interstitial Lung Disease (2%)
- Lung Disorder (4%)
- Rhinitis (2%)

Skin and Appendages:
- Pruritus (2%)

Special Senses:
- Cataract (2%)
- Photophobia (2%)

Laboratory Values:
- Haptoglobin Increased (2%)
- Leukopenia (3%)
- Alkaline Phosphatase Increased (3%)
- BUN Increased (2%)
- Creatinine Increased (2%)
- Hyperglycemia (4%)

OVERDOSAGE

One case of massive overdosage has been published. A 79-year-old man attempted suicide by ingesting 13 g of nilutamide (i.e., 43 times the maximum recommended dose). Despite immediate gastric lavage and oral administration of activated charcoal, plasma nilutamide levels peaked at 6 times the normal range 2 hours after ingestion. There were no clinical signs or symptoms or changes in parameters such as transaminases or chest X-ray. Maintenance treatment (150 mg/day) was resumed 30 days later.

In repeated-dose tolerance studies, doses of 600 mg/day and 900 mg/day were administered to 9 and 4 patients, respectively. The ingestion of these doses was associated with gastrointestinal disorders, including nausea and vomiting, malaise, headache, and dizziness. In addition, a transient elevation in hepatic enzyme levels was noted in one patient.

Since nilutamide is protein bound, dialysis may not be useful as treatment for overdose. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The recommended dosage is 300 mg once a day for 30 days, followed thereafter by 150 mg once a day. Nilutamide Tablets can be taken with or without food.

HOW SUPPLIED

Nilutamide Tablets, 150 mg, are supplied in boxes of 30 tablets. Each box contains 3 child-resistant, PVC, aluminum foil-backed blisters of 10 tablets (NDC 62559-173-31). Each round, biconvex, white to off-white tablet is debossed with “ANI” and “173” on one side and plain on the other side.

Store at 25°C (77°F); excursions permitted between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light.

Manufactured by:

ANI Pharmaceuticals, Inc.
Baudette, MN 56623

ani Pharmaceuticals, Inc.

9625 Rev 12/15

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	12/10/2015
ANDA Number(s)	207631
Review Number	2
Applicant Name	ANI Pharmaceuticals, Inc
Established Name & Strength(s)	Nilutamide Tablets, 150 mg
Proposed Proprietary Name	Not applicable
Submission Received Date	11/10/2015 Response to ECD
Labeling Reviewer	Sarah Kurtz
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Not applicable

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated November 10, 2015.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

CARTON: Bold storage statements and "Protect from light."

PRESCRIBING INFORMATION
Please ensure your revision date reflects the date revised (i.e., prescribing information indicates revision date 12/2015; however, submission date 11/2015).
DESCRIPTION/Inactive Ingredients: (b) (4)
INDICATIONS and USAGE: Revise the second sentence to read (b) (4)

STRUCTURED PRODUCT LABELING (SPL): Revise Data Elements/Product Characteristics, color to read "WHITE (white to off-white)".

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The below comments are from the labeling review C1 based on the submission dated 06/18/2014.

Please make the following revisions:

1. Container Label (blister) **Satisfactory**
   a. [redacted] the established name to read "Nilutamide Tablet" on individual blisters.
   b. Include a bar code to identify each blister if your drug product is for [redacted] dispensing.
2. Carton Labeling **Satisfactory**
   a. Please indicate if the drug product is intended for dispensing [redacted] as unit of use packaging. We note your statement in 2.3.P.2.4, the "product should have the same container closure attributes as that of RLD"; however, please specify whether your container or carton are child resistant. Please note if your product is unit of use, the blister packaging should be child-resistant.
   b. Revise the net quantity statement to read [redacted] "30 (3 x 10) Unit of Use Tablets" as applicable.
3. Prescribing Information **Satisfactory**
   a. We note you list the starch as [redacted] starch. [redacted]
   b. Consider replacing hyphens with "to" when referencing a range of numbers (e.g., "…15 to 30°C (59 to 86°F)…").
   c. [redacted] package insert and revise the remaining date to reflect the actual revision date.
   d. Description
      Revise the last sentence to read "Each Nilutamide Tablet contains…"
   e. Warnings
      [redacted] the "Interstitial Pneumonitis" heading [redacted] the last sentence "**If symptoms occur…determined if the symptoms are drug related.**"
   f. Information for Patients:
      Bold the paragraph beginning "**In clinical trials, 13% to 57% of patients… alleviated by the wearing of tinted glasses.**"
   g. Carcinogenesis, Mutagenesis, Impairment Of Fertility
      Create a new paragraph [redacted] "Nilutamide displayed no mutagenic effects in a variety of in vitro and in vivo tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests)."
   h. Animal Pharmacology and Toxicology
      i. Create a new paragraph with the sentence "Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1–2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis)."
      ii. Create a new paragraph with the sentences "The hepatic and pulmonary adverse effects… P450 reductase in the lungs and liver of rats and humans."
   i. How Supplied
      Revise the first sentence to read "Nilutamide Tablets, 150 mg, are…"
4. Structured Product Labeling (SPL) **Satisfactory**

a. Revise Inactive Ingredients to accurately reflect ingredients in the product (b) (4) SPL data elements states (b) (4)
b. Revise Product Characteristics to reflect description in How Supplied section "white to off-white". **Requesting post-approval.**
c. Revise Package Description to read (b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review? **NO** If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Satisfactory in submission 11/10/2015

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

S-007 (09/25/2015): CMC supplement- an alternate site for the manufacture of Nilandron (nilutamide) tablets along with accompanying changes in the manufacturing process due to site practices and equipment
S-006 (08/13/2014): CMC supplement- alternative site for the manufacture of nilutamide drug substance
S-005 (08/04/2005): CMC supplement- changes in the manufacturing and controls of the drug substance, nilutamide

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Are there any pending issues in DLR's SharePoint Drug Facts? NO **If Yes, please explain**
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)		
☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG		
NDA 020169	Proprietary Name: NILANDRON®	

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)	
S- 003 July 26, 2004	**Description of Supplement:** This supplement is in response to an action letter requesting the following revisions: The proposed modifications to the labeling provided in S-003 are acceptable except for the new General subsection in the PRECAUTIONS section of the package insert. Based on the information submitted in S-003, the Division recommends inserting the following General subsection in the PRECAUTIONS section of the Nilandron package insert: PRECAUTIONS General Antiandrogen Withdrawal Syndrome Patients whose disease progresses while being treated with an antiandrogen may experience clinical improvement with discontinuation of the antiandrogen.
Other	We note the last approved RLD NDA package insert is not available on Drugs@FDA. The last approved NDA supplement was NDA 020169/S-003; however, the firm submitted the requested revisions 12/23/2005. This revised submission was compared with Annual Report 17 (11/15/2013) to identify modifications for consideration during the side-by-side analysis of insert labeling. (b) (4) (b) (4)

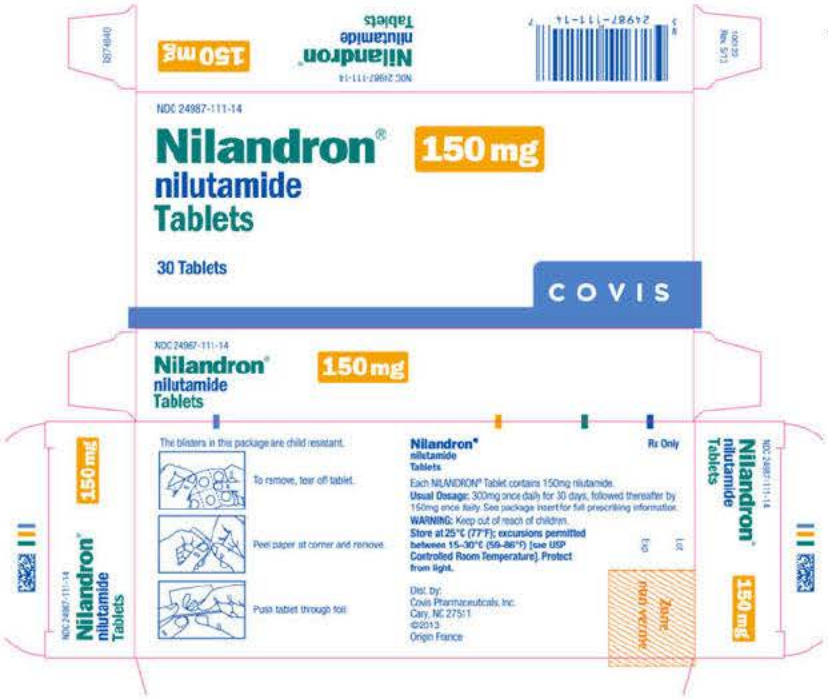
Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

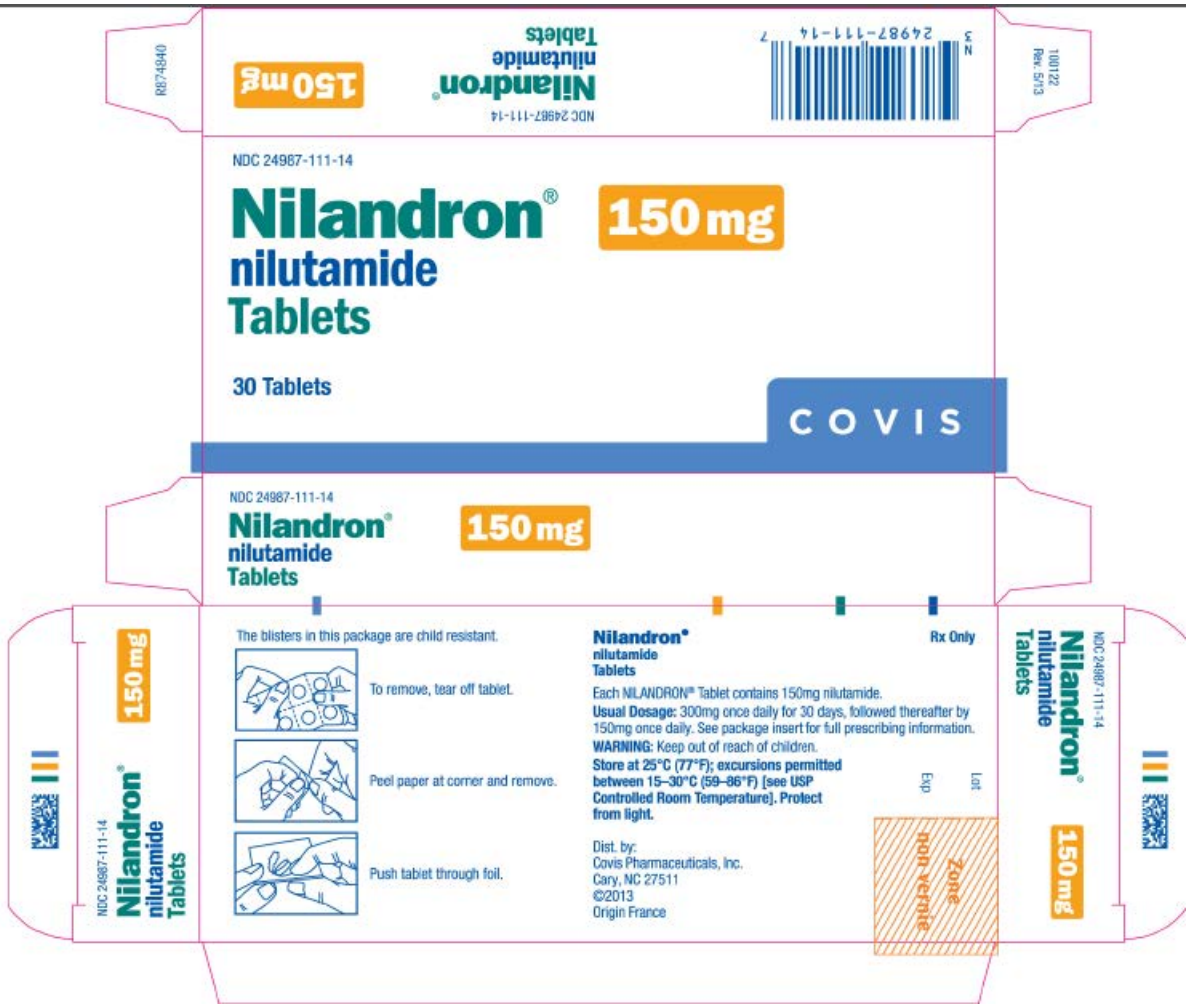
Reviewer Comments: N/A

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DailyMed 06/2014]



DARRTS (AR-017 11/2013)


NDC 24987-111-14
Nilandron®
150 mg
nilutamide
Tablets
30 Tablets
COVIS
The blisters in this package are child resistant.
To remove, tear off tablet.
Peel paper at corner and remove.
Push tablet through foil.
Nilandron®
nilutamide
Tablets
Rx Only
Each NILANDRON® Tablet contains 150mg nilutamide.
Usual Dosage: 300mg once daily for 30 days, followed thereafter by 150mg once daily. See package insert for full prescribing information.
WARNING: Keep out of reach of children.
Store at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.
Dist. by:
Covis Pharmaceuticals, Inc.
Cary, NC 27511
©2013
Origin France
Lot
Exp
Zone non vernie
Rev. 5/13


NDC 24987-111-14
Nilandron®
(nilutamide) Tablets
150 mg Rx Only
Covis Pharmaceuticals, Inc.
Origin France 100121
Lot Exp
R605230

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	12/10/2015	No	N/A	N/A
PF	12/14/2015	No	N/A	N/A

Reviewer Comments: N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/14/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	Each Nilutamide Tablet contains 150 mg of nilutamide. The inactive ingredients in Nilutamide Tablets include: calcium stearate, docusate sodium, lactose, povidone, corn starch, and talc.	Minor revisions to insert labeling.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	HOW SUPPLIED Nilutamide Tablets, 150 mg, are supplied in boxes of 30 tablets. Each box contains 3 child resistant, PVC, aluminum foil-backed blisters of 10 tablets (NDC 62559-173-31). Each round, biconvex, white to off-white tablet is debossed with "ANI" and "173" on one side and plain on the other side. Store at 25°C (77°F); excursions permitted between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light.	Applicant noted packaging to be child-resistant.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Consistent with previously reviewed labeling.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: N/A

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: N/A

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column,

you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	NA			
Blister	Final	(b) (4)	11/10/2015	Satisfactory
Carton	Final	30 (3 x 10) Unit-of-Use	11/10/2015	Satisfactory
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	12/2015;9625	11/10/2015	Satisfactory
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements		11/2015	11/10/2015	Satisfactory

***** This document contains proprietary information that cannot be released to the public*****

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	10/03/2014
ANDA Application Number	207631
Review Cycle Number	1
Applicant Name	ANI Pharmaceuticals, Inc.
Established Name	Nilutamide Tablets
Strength(s)	150 mg
Proposed Proprietary Name	N/A
DARRTS Received Date	06/18/2014
Labeling Reviewer	Sarah Kurtz
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ No Comments – The Labels and Labeling are ready for

☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Please make the following revisions:

1. Container Label (blister)
   a. [redacted] the established name to read "Nilutamide Tablet" on individual blisters.
   b. Include a bar code to identify each blister if your drug product is for [redacted] dispensing.
2. Carton Labeling
   a. Please indicate if the drug product is intended for dispensing [redacted] as unit of use packaging. We note your statement in 2.3.P.2.4, the "product should have the same container closure attributes as that of RLD"; however, please specify whether your container or carton are child resistant. Please note if your product is unit of use, the blister packaging should be child-resistant.
   b. Revise the net quantity statement to read [redacted] "30 (3 x 10) Unit of Use Tablets" as applicable.
3. Prescribing Information
   a. We note you list the starch as [redacted] starch. Please include the [redacted]
   b. Consider replacing hyphens with "to" when referencing a range of numbers (e.g., "…15 to 30°C (59 to 86°F)…").
   c. [redacted] package insert and revise the remaining date to reflect the actual revision date.
   d. Description
      Revise the last sentence to read "Each Nilutamide Tablet contains…"
   e. Warnings
      [redacted] the "Interstitial Pneumonitis" heading [redacted] the last sentence "**If symptoms occur…determined if the symptoms are drug related.**"
   f. Information for Patients:
      Bold the paragraph beginning "**In clinical trials, 13% to 57% of patients… alleviated by the wearing of tinted glasses.**"
   g. Carcinogenesis, Mutagenesis, Impairment Of Fertility
      Create a new paragraph [redacted] "Nilutamide displayed no mutagenic effects in a variety of in vitro and in vivo tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests)."
   h. Animal Pharmacology and Toxicology
      i. Create a new paragraph with the sentence "Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1–2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis)."
      ii. Create a new paragraph with the sentences "The hepatic and pulmonary adverse effects… P450 reductase in the lungs and liver of rats and humans."
   i. How Supplied
      Revise the first sentence to read "Nilutamide Tablets, 150 mg, are…"
4. Structured Product Labeling (SPL)

a. Revise Inactive Ingredients to accurately reflect ingredients in the product [redacted] (b) (4) SPL data elements states [redacted] (b) (4)
b. Revise Product Characteristics to reflect description in How Supplied section “white to off-white”.
c. Revise Package Description to read [redacted] (b) (4)

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the last submitted labeling and all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1. MODEL LABELING FOR ANDA

1.1 MODEL CONTAINER LABELS FOR ANDA
1.2 PRESCRIBING INFORMATION MODEL LABELING

2. MATERIAL ANALYSIS

2.1 GENERAL

2.1.1 Established Name Assessment
2.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

2.2 CONTAINER LABEL

2.2.1 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors
2.2.2 Other Container Label Considerations
2.2.3 Container Label for Small Volume Parenteral Solutions:
2.2.4 Container Label for Sterile Solid Injectable:
2.2.5 Container Label for Pharmacy Bulk Package:
2.2.6 Unit Dose Blister Labels
2.2.7 Over The Counter (OTC) Label
2.2.8 Presentation of Manufacturer/Distributor/Packer on Labeling
2.2.9 Description of the Container/Closure
2.2.10 Storage and Dispensing Recommendations
2.2.11 Related Applications Containing the Same Active Ingredient
2.2.12 Comparison of ANDA Inactive Ingredients that Require Special Labeling Statements to Model

2.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING
2.4 PRESCRIBING INFORMATION

2.4.1 Patents and Exclusivities
2.4.2 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)
2.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)
2.4.4 How Supplied Section
2.4.5 Previous Labeling Reviews for ANDA and/or Related Correspondence

2.5 MEDICATION GUIDE
2.6 OTHER PATIENT LABELING
2.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

3.1 ANDA LABELS AND LABELING SUBMITTED

4. QUESTIONS AND COMMENTS FOR CLICK HERE TO ENTER TEXT.
5. SPECIAL CONSIDERATIONS
6. POST APPROVAL REVISIONS

1. MODEL LABELING FOR ANDA

Our review is based on the following model labels and labeling used for comparison to the submitted ANDA labeling.

1.1 MODEL CONTAINER LABELS FOR ANDA

In Table 1 below, check all sources for Model container labels and carton labeling (secondary packaging) that applies.

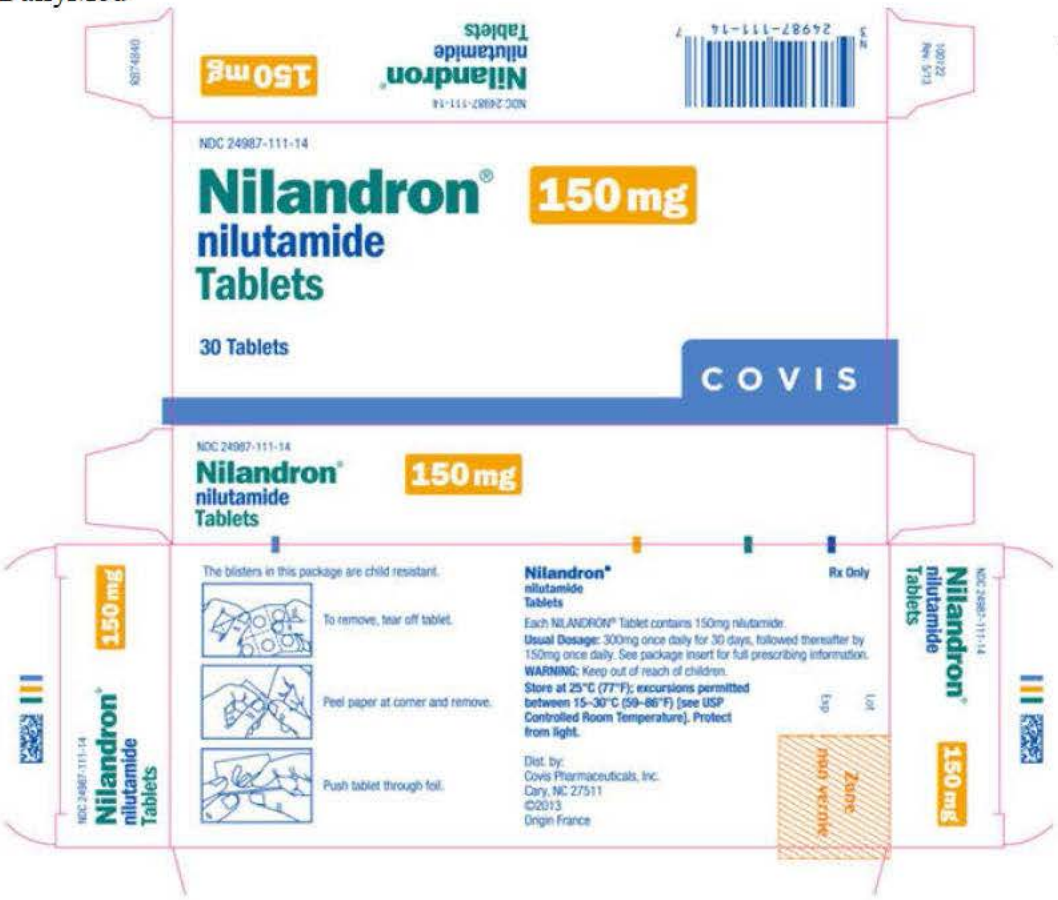
Container labels are assessed in section 2.2.

Carton labeling (outer or secondary packaging) is assessed in section 2.3.

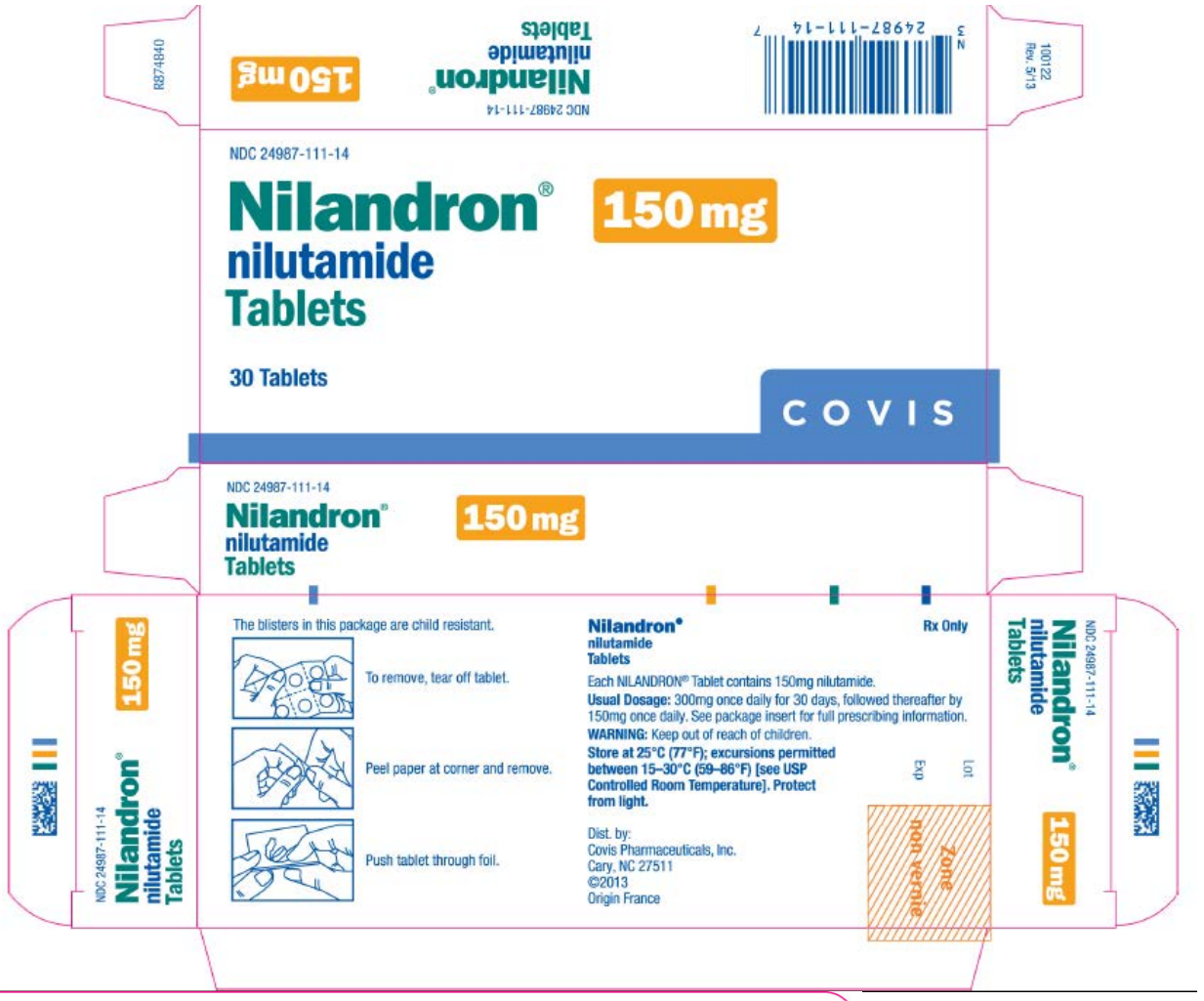
Table 1: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply)	
Source	**Date of source document (i.e. supplement approval date, annual report date)**
☒ DailyMed	06/2014
☒ Annual Report 17	11/15/2013

Model labels and carton labeling. [Insert or paste images below]

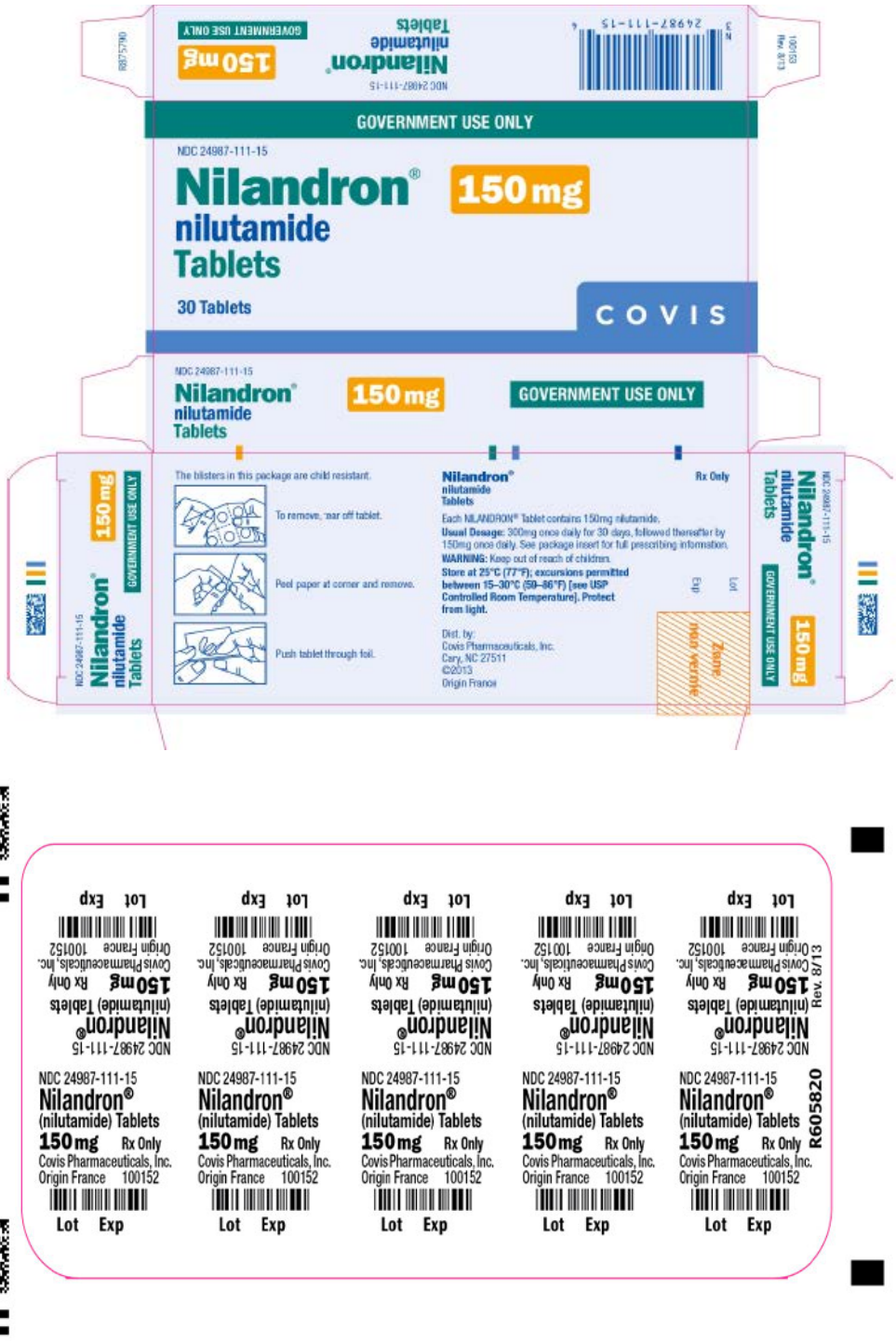
DailyMed



DAARTS (Annual Report 17)



Government Blister and Carton



1.2 PRESCRIBING INFORMATION MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 2.

Prescribing information is assessed in section 2.4.

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)		
☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG		
NDA 020169	**Proprietary Name**: NILANDRON®	
S- 003 July 26, 2004	**Description of Supplement**: This supplement is in response to an action letter requesting the following revisions: The proposed modifications to the labeling provided in S-003 are acceptable except for the new General subsection in the PRECAUTIONS section of the package insert. Based on the information submitted in S-003, the Division recommends inserting the following General subsection in the PRECAUTIONS section of the Nilandron package insert: PRECAUTIONS General Antiandrogen Withdrawal Syndrome Patients whose disease progresses while being treated with an antiandrogen may experience clinical improvement with discontinuation of the antiandrogen.	
Other	We note the last approved RLD NDA package insert is not available on Drugs@FDA. The last approved NDA supplement was NDA 020169/S-003; however, the firm submitted the requested revisions 12/23/2005. This revised submission was compared with Annual Report 17 (11/15/2013) to identify modifications for consideration during the side-by-side analysis of insert labeling. (b) (4) (b) (4)	

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant (Page 2).

2.1 GENERAL

2.1.1 Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

Table 3: Comparison of Established Names

Model Labeling: NILANDRON® (nilutamide) Tablets
ANDA: Nilutamide Tablets
USP: Not applicable

Reviewer Assessment:

Is the established name for ANDA acceptable? **YES**
Is the established (and proprietary name) displayed in a manner consistent 21 CFR 201.10? **YES**
Is title case used in established name? **YES**
Is established name on list of name pairs that use Tall Man lettering found on FDA webpage? **NO**

- If yes does labeling comply with Tall Man lettering recommendations? **NA**

Reviewer Comments:

2.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 4.

Table 4: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Labeling statements found NA if no monograph
USP	10/3/2014	**NO**	N/A
PF	10/3/2014	**NO**	N/A

Reviewer Assessment:

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements? **NO**
Do required labeling statements appear on/in the ANDA labeling? **NA**
Are the USP packaging and storage recommendations reflected in the labels and labeling? **NA**

Reviewer Comments:

2.2 CONTAINER LABEL

We evaluated the container labels for the inclusion of all required statements and safety considerations.

2.2.1 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

We used the draft Guidance for Industry titled Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors for the following assessment.

Reviewer Assessment:

Does the following information appear as the most prominent information on the Principal Display Panel?
- Proprietary name? **NA**
- Established name? **YES**
- Product strength? **YES**
- Route(s) of administration (other than oral)? **NA**
- Warnings (if any) or cautionary statements (if any)? **NA**

Does the following information appear of lesser prominence on the Principal Display Panel?
- Rx-only statement? **YES**
- Net quantity statement? **YES**
- Manufacturer logo? **YES**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **NO** (blister pack revisions)

Reviewer Comments:

2.2.2 Other Container Label Considerations

Reviewer Assessment:

Does this container meet the "too small" exemption found in 21 CFR 201.10(i)? **YES** (blister pack)
Are all abbreviations acceptable? (i.e., mg, mcg, HCl)? **YES**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Does the net quantity statement appear separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)? **YES**
Are the rules governing leading and terminal zeroes, decimals, and commas followed? **YES**
If other than oral use, is the route of administration correctly described? **NA**
Are all required warning statements that appear on Model Label properly displayed? **NA**
Is space provided to display expiration date properly? **YES**
Is bar code properly displayed per 21 CFR 201.25(c)(2)? **YES**
Is NDC properly displayed? **YES**
Is controlled substance symbol properly displayed? **NA**
Is the "Usual Dosage" on side panel and is it acceptable? **YES**
Is a product strength equivalency statement on side panel? **NA**
Are the Medication Guide Pharmacist instructions included per 208.24(d)? **NA**

Reviewer Comments:

2.2.3 Container Label for Small Volume Parenteral Solutions:

Is container for small volume parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.4.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength?**NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

2.2.4 Container Label for Sterile Solid Injectable:

Is container for sterile solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstituting the product and the resultant concentration if space permits? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

2.2.5 Container Label for Pharmacy Bulk Package:

Is container a Pharmacy Bulk Package? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.6.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

(b) (4)

[redacted]

2.2.7 Over The Counter (OTC) Label

Is this label for an OTC product? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.8

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does packaging meet the requirements for Special Packaging under the Poison Prevention Act and defined per 16 CFR 1700? **NA**
Does packaging meet the tamper-evident requirements 21 CFR 211.132? **NA**
Does "Questions?" have a toll-free number no less than size 6 pt. font per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" [21 CFR 201.66 (c)(5)(vii)]? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

Reviewer Comments:

2.2.8 Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations (21 CFR 201.1).

Table 5 provides a description of this comparison. [NOTE: This presentation/assessment may apply to other labeling submitted].

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of Facility ANDA Manufactured	**2.3.P.3** DRUG PRODUCT Name: ANI Pharmaceuticals, Inc Address: (b) (4) Facility ID No.: Function/ Responsibility:
Name and Address on ANDA Labels	**Carton:** Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623 **Blister:** ANI Pharmaceuticals, Inc.
Name and Address on ANDA Labeling	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623

Reviewer Assessment:

Does the labeling have the required qualifiers per 21 CFR 201.1? **YES**
For Foreign manufacturers, does the labeling have the country of origin? **NA**
For Foreign manufacturers, does the labeling have a US contact/distributor? **NA**

Reviewer Comments:

2.2.9 Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**

(b) (4)

Are the tamper evident requirements met for OTC and Controlled Substances? **NA**
Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**
For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? Not applicable
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Comment
-We will request the Applicant verify if the container closure is child-resistant and revise labels/labeling accordingly.
-We note the blister packaging is required to be child-resistant if the packaging is unit of use and will therefore request the Applicant clarify (b) (4) unit of use.
2.3.P.2.4

COMPARISON OF PACKAGING CONFIGURATION (TEST VS RLD)	
NILANDRON® Tablet *(RLD)*	
Product	Carton of 3 Blister Cards of 10 Tablets/card
Blister Film	PVC (b) (4) aluminum foil-backed blisters
Nilutamide Tablets, 150 mg (Test)	
Product	Carton of 3 Blister Cards of 10 Tablets/card
Blister Film	(b) (4)

Comment: The containers tested meet the USP specifications for Class A Unit Dose Containers.

2.2.10 Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 6). [NOTE: This assessment may apply to other labeling submitted]

Table 6: Model Labeling and ANDA Storage/Dispensing Recommendations
Model Labeling
Insert: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.
Container (blister): none **Carton**: Store at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.
ANDA
Carton: Store at 25ºC (77ºF); excursions permitted to 15º -30ºC (59º -86ºF). [See USP Controlled Room Temperature] Protect from light. **Blister**: none
Insert: Store at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.
USP
Not applicable

Reviewer Assessment:

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NA**
Are the storage temperature recommendations acceptable? **YES**
Does the temperature statement conform to the OGD format for controlled room temperature? **YES**

Reviewer Comments:

2.2.11 Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

Reviewer Assessment:

Are the labels and labeling of these products differentiated to avoid selection errors? **NA**

Reviewer Comments:
-We note the Applicant (ANI) does not currently have additional submissions for any formulation of nilutamide, 10/03/2014.

2.2.12 Comparison of ANDA Inactive Ingredients that Require Special Labeling Statements to Model

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 7.

NOTE: This section is for assessing required statements on container labels only for both prescription and OTC drug products. Required statements for prescribing information is assessed for Prescription drug products in Sections 2.4.2 and 2.4.3

Table 7: Inactive Ingredients contained in Model Product and ANDA that require special labeling statements	
Model Labeling	**ANDA**
N/A	**N/A**

Reviewer Assessment:

Do any of the inactive ingredients need a label statement required by regulations? **NO**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**

Reviewer Comments:

2.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Do all required label statements and safety considerations assessed above for CONTAINER labels appear on the carton? **NO**
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**

(b) (4)

If country of origin is not on Container, does appear on outer packaging labeling? **NA**

Reviewer Comments:
-We will request the Applicant indicate whether blisters are child-resistant and revise labels/labeling accordingly.

2.4 PRESCRIBING INFORMATION

Reviewer Assessment:

Are the labeling contained in the submission the same as the review model labeling? **NO**
Are the differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NO**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:
-We note the RLD NDA 020169 package insert labeling is not available through Drugs@FDA and therefore we compared the RLD Annual Report -17 with the RLD last approved labeling (2004), prior to completing the side-by-side.

(b) (4)

2.4.1 Patents and Exclusivities

Are there any unexpired patents or marketing exclusivities for Model Labeling? **NO**

If YES go to the table and assessments below.
If NO go to section 2.4.2.
Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 8: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	How Applicant Filed	Labeling Impact
N/A					

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Patent and Exclusivity Search Results from query on Appl No 020169 Product 002 in the OB Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling			
Exclusivity Code	**Exclusivity Code Definition**	**Exclusivity Expiration**	**Labeling Impact**
N/A			

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

2.4.2 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)

Is submitted labeling for a topical or oral product? **YES**

If YES, complete tables 10a, 10b, and 10c along with assessment below.
If NO, go to section 2.4.3.
We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

In Table 10a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 10a: Inactive Ingredients contained in Model Product and ANDA from Description section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
corn starch	(b) (4)
lactose	lactose
povidone	povidone,
docusate sodium	docusate sodium
magnesium stearate	calcium stearate
talc	talc

In Table 10b we compared the lists of inactive ingredients in the DESCRIPTION section (b) (4) in ANDA.

Table 10b: Comparison Inactive Ingredients contained in ANDA Description section (b) (4)

Description Section	(b) (4)
(b) (4)	
lactose	
povidone	
docusate sodium	
calcium stearate	
talc	

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 10c.for Model and ANDA

Table 10c Specific inactive ingredients that require special warnings, precautions

Table 10c Specific inactive ingredients that require special warnings, precautions	
Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
N/A	N/A

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the ANDA? **NO**
Are the required labeling statements present in the ANDA labeling? **NA**

Reviewer Comments:

2.3.P.2.2

(b) (4) RLD VS TEST PRODUCT	
Reference Listed Drug	**Test Product**
Corn Starch	(b) (4)
Lactose	Lactose (b) (4) NF
Povidone	Povidone, USP
Docusate Sodium	Docusate Sodium, USP
Magnesium Stearate	Calcium Stearate, NF
Talc	Talc, USP

(b) (4)

-We will request consistency between the Description section and Component and Composition.

2.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)

Is submitted labeling for an ophthalmic, injectable, or an otic product? **NO**

If YES, complete tables 11a, 11b, and 11c along with the assessment below.
If NO go to section 2.4.4.

We compared the list of inactive ingredients and the amount of the inactive ingredient contained in this product as to those contained in the Model Labeling to determine if all components and composition are the same and if they are listed accurately in the labeling.

In Table 11a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 11a: Inactive Ingredients contained in Model Product and ANDA from Description section	
Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
N/A	N/A

In Table 11b we compared the lists of inactive ingredients in the DESCRIPTION section and Components and Components statements in ANDA.

Table 11b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

Description Section	Components and Composition
N/A	N/A

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 11c.for Model and ANDA

Table 11c Specific inactive ingredients that require special warnings, precautions

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
N/A	N/A

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the application? **NA**
Are the required labeling statements present in the ANDA labeling? **NA**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**

Reviewer Comments:

2.4.4 How Supplied Section

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as coring configuration, are highlighted in Table 12 and will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based on the ANDA finished product description.

Table 12: Comparison of Model Labeling to ANDA finished product

Model Labeling

HOW SUPPLIED

NILANDRON 150 mg tablets are supplied in boxes of 30 tablets. Each box contains 3 child-resistant, PVC, aluminum foil-backed blisters of 10 tablets (NDC 24987-111-14 & 24987-111-15). Each white, biconvex, cylindrical (10 mm in diameter) tablet has a triangular logo on one side and an internal reference number (168D) on the other.

Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

ANDA

HOW SUPPLIED

Nilutamide Tablets 150 mg are supplied in boxes of 30 tablets. (b) (4) Each round, biconvex, white to off-white tablet is debossed with "ANI" and "173" on one side and plain on the other side.

Store at 25°C (77°F); excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

2.3.P.2.4

DRUG PRODUCT FORMULATION			
		QUANTITY	
INGREDIENT	AMOUNT/ DOSE	EXHIBIT BATCH (b) (4)	COMMERCIAL BATCH (b) (4)
Nilutamide (b) (4)	150.0 mg (b) (4)		
Lactose (b) (4) NF (b) (4)			
Povidone, USP (b) (4)			
Docusate Sodium, USP (b) (4)			
(b) (4)			
Talc, USP			
Calcium Stearate, NF			
TOTAL WEIGHT	**400 mg**		

(b) (4)

Reviewer Assessment:

Is the description (scoring, color, and imprint) of the finished product accurate in the HOW SUPPLIED section of the insert? **YES**

Are the packaging sizes acceptable as compared to the Model Labeling? **YES**

Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data? **NO**

Reviewer Comments:

2.4.5 Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 13 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

Table 13: Completed Labeling Reviews or Other Correspondence for Application Under Review

Search Date	Finalized Date of DARRTS Document	Were Previous Comments Addressed? (Yes/No/Explain)
N/A		

2.5 MEDICATION GUIDE

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container and carton labeling.

Reviewer Assessment:

Does the format meet the requirements of 21 CFR 208.20? **NA**
Are the dispensing and distributions requirements of 21 CFR 208.24 met? **NA**
Has the Applicant committed to provide a sufficient number of medication guides? **NA**
Is the phonetic spelling of the proprietary or established name present? **NA**
Is the dispensing directive present on the container and carton labeling? **NA**
Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments:
-We note Nilutamide tablets do not require a Medication Guide or REMS.

2.6 OTHER PATIENT LABELING

Not applicable

2.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

Table 14: Comparison of Model and ANDA Tablet/Capsule Size

Model Labeling	Score no score Size 10mm
ANDA Labeling	Score no score Size (b) (4)

Reviewer Assessment:

Are the data elements consistent with the information submitted in the ANDA? **NO**
Is the tablet/capsule size similar to the RLD? **YES**

Reviewer Comments:

-We will request the Applicant revise Inactive Ingredients to accurately reflect ingredients in product (Package insert lists (b) (4) rather than corn starch on the SPL).

-We will request the Applicant revise Product Characteristics to reflect description in How Supplied section "white to off-white".

-We will request the Applicant revise the Package Description to read (b) (4)

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 15 and 16 provide a summary of recommendations for each material analyzed in this review.

Table 15: Review Summary of Container Label and Carton Labeling			
	Packaging Sizes	**Submission Date**	**Recommendation**
Blister ☒ **Draft** ☐ **FPL**	(b) (4)	06/18/2014	☐ Satisfactory ☒ Revise
Carton ☐ **Draft** ☒ **FPL**	3 x 10 blister packs (30s)	06/18/2014	☐ Satisfactory ☒ Revise
Table 16 Review Summary of Prescribing Information and Patient Labeling			
	Revision Date and/or code	**Submission Date**	**Recommendation**
Prescribing Info ☒ **Draft** ☐ **FPL**	(9625 Rev MM/YY)	06/18/2014	☐ Satisfactory ☒ Revise
SPL ☒	01/2014	06/18/2014	☐ Satisfactory ☒ Revise

3.1 ANDA LABELS AND LABELING SUBMITTED

(b) (4)


(b) (4)

4. QUESTIONS AND COMMENTS FOR CHEMISTRY

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

Reviewer Assessment:

Does the response(s) received require a label and/or labeling revision? **N/A**
Reviewer Comments:

APPEARS THIS WAY ON ORGINAL

5. SPECIAL CONSIDERATIONS

Not applicable

APPEARS THIS WAY ON ORIGINAL

6. POST APPROVAL REVISIONS

Not applicable

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

CHEMISTRY REVIEWS

CHECKLIST FOR THE CHEMISTRY REVIEW:
ANDA 207631, Nitulamide Tablets, (b) (4) and 150 mg.

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	sy 7/12/16	☐ Yes ☒ No
DMF adequate?	sy 7/12/16	☒ Yes ☐ No *(see comments)
Any outstanding consults?	sy 7/12/16	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	BC – LRN 7/14/2016	☒ Yes ☐ No ☐ N/A
Are all facility inspections acceptable?	sy 7/12/16	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	sy 7/12/16	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	BC – LRN 7/14/2016	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	BC – LRN 7/14/2016	☐ Yes ☒ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	sy 7/12/16	☒ Yes ☐ No
(b) (4)		

Division IRP I/Branch III	Signature	Date
Laxma R Nagavelli, PhD		7/14/2016

Overall Manufacturing Inspection Recommendation

If you are finished with this task, change the Task Status to Complete.

Task Summary | Task Details | Documents | Approvals | Updates | Application Life Cycle | **Inspection Management Form**

As of Jul 12, 2016 9:58 am GMT

Inspection Management Form

ANDA-207631-ORIG-1

ANI PHARMACEUTICALS INC | 2111358 | TCM TABLETS, PROMPT RELEASE | Approve Facility

PACE ANALYTICAL LIFE SCIENCES, LLC | 3001452367 | CTL CONTROL TESTING LABORATORY | Approve Facility

RICONPHARMA LLC | 3007236518 | CTL CONTROL TESTING LABORATORY | Approve Facility

KEKULE PHARMA LIMITED | 3009261338 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS |

Overall Manufacturing Inspection Recommendation

- (•) Approve
- ( ) Withhold

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

- First Generic? Yes: ☒ No: ☒
- MR Product? Yes: ☐ No: ☒
- Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change? Yes: ☐ No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☐ **2 Tier:** ☒

C. Approvability: –*CMC is acceptable*

ANDA 207631

Nilutamide Tablets, 150 mg

ANI Pharmaceuticals, Inc.

Kadum Al Shareffi, Ph.D.
Office of Life Cycle Drug Products
Division of IR Products 1
Branch 3

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Chemistry Review Data Sheet

1. ANDA: 207631

2. REVIEW #: 1

3. REVIEW DATE: 04-27-2015 / 12-04-2015/ 12-08-2015 / 05-06-2016 / 05-11-2016

4. REVIEWER: Kadum Al Shareffi, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Correspondence	03-18-2016
Quality /Response to Information Request	01-27-2016
Response to ECD-Labeling	11-10-2015
Amendment to the IR letter dated Apr 30, 2015	05-28-2015
Quality –Stability Information	09-25-2014
Original Submission	06-18-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	ANI Pharmaceuticals, Inc (FEI; 2111358)
Address: Applicant's Responsible Official Telephone: Fax; Email;	210 Main Street West, Baudette MN 56623 USA 218-634-3500* 888-519-0459 Ellen Camos, Director of Regulatory Affairs (b) (6) / 218-634-3638 888.519.0459 ellen.camos@anipharmaceuticals.com
Representative:	David J. Sullivan, Ph.D / Director, Regulatory Affairs Tel: 218-634-3507 Fax: 218-634-3540 Email: david.sullivan@anipharmaceuticals.com

*Tel no. has changed, by amendment dated 11-10-2015

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Nilutamide Tablet

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Nilandron® Tablet (Nilutamide)
Innovator Company: Covis Pharma SARL (Sanofi Aventis USA)
(NDA # 020169, approved April 30, 1999)
Patent data: There are no unexpired patents for this product
Exclusivity Data: There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __ Rx __ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

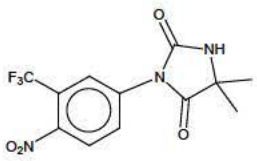
☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5, 5-dimethyl-3-(4-nitro-3-(trifluoromethyl) phenyl) imidazolidine-2, 4-dione
Molecular formula: $C_{12}H_{10}F_3N_3O_4$
Molecular weight: 317.25
CAS number: 63612-50-0
Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate with IR	05-11-2016	Fatima Sequeira
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Nilandron® (Nilutamide Tablet 150 mg)	NDA 020169 (Covis Pharma SARL / Sanofi Aventis USA)	RLD

18. STATUS

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
Methods Validation		N/A		
EES		Approve facility	03-11-2016	Laura Fontan
Labeling		Acceptable – Include post approval comments	12-14-2015	Sarah Kurtz
Bioequivalence	Dissolution	Adequate	09-28-2014	Nabeel Babaa
	Bioequivalency	Adequate	10-11-2014	Eunjung Park
Toxicology/Clinical		N/A		
EA		Acceptable	9-23-2015	Kadum Al Shareffi
Radiopharmaceutical		N/A		
Samples Requested		A/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			

Chemistry Review Data Sheet

(b) (4)

*Registration (FEI) number, contact, the telephone number, and email for drug substance manufacturing has been changed, Amendment dated 03-18-2016

Executive Summary Section

Chemistry Review for ANDA 207631

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC of this ANDA is acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a. Drug Substance

Nilutamide is not an official USP monograph, but European Pharmacopeia (EP) has a monograph for Nilutamide. It is a microcrystalline, white to practically white powder with a molecular weight of 317.25. Its molecular formula is $C_{12}H_{10}F_3N_3O_4$. It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [<0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

b. Drug Product

There is no monograph in USP for Nilutamide tablet drug product.

(i) Description of drug product

Nilutamide Tablet 150 mg is round biconvex, white to off-white, debossed with "ANI" and "173" on one side and plain on the other side.

(ii) Components of drug product

Active ingredient: Nilutamide

Inactive ingredients: (b) (4) Lactose (b) (4) Povidone, Docusate sodium, (b) (4) and Calcium stearate.

(iii) Manufacturing process of drug product

(b) (4)

Compression

(iv) Test method for drug product

The drug product is tested using in-house and USP methods. The HPLC methods for Assay and for related substances are validated or verified as appropriate. ANI accepted the recommendation of the DB II specification of the dissolution limit of release of Nilutamide to (b) (4) in the amendment dated 9-25-2014. The dissolution is adequate per DBE.

(v) Executed batch and proposed production batches

Strength	Exhibit batch		Intended commercial batch		Scale-up Factor
	Batch size	Batch size (unit)	Batch size	Batch size (unit)	
Nilutamide Tablets 150 mg	(b) (4)				

(vi) Packaging

PROPOSED COMMERCIAL PACKAGING FOR GENERIC NILUTAMIDE TABLETS, 150 MG	
Product	Carton of 3 Blister Cards of 10 Tablets/card
Blister Film	(b) (4)

(vii) Storage conditions

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature] Protect from light. (b) (4)

(viii) Expiration Date

The proposed expiration data for the drug product is (b) (4) for the proposed marketing container/closure system, (b) (4) (b) (4)

The firm provided 12 months of CRT Stability data and 6 months of accelerated stability data for all the packaging. All monitored attributes of the drug product are within the established specifications. No unfavored trend was observed.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS

For use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

HOW SUPPLIED

Nilutamide Tablet 150 mg is supplied in boxes of 30 tablets. (b) (4)

NDC 62559-173-31

ICH Guideline Q3A for Drug substance and Q3B for Drug product of **MDD of 300 mg:**

	ICH Identification threshold	ICH Qualification threshold
Drug substance	0.10%	0.15%
Drug product	0.2%	0.2%

C. Initial and Updated Risk Assessment

(b) (4)

[redacted]

D. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is acceptable. Dissolution is Adequate, Bioequivalence is Adequate. Labeling is Acceptable – Include post approval comments. EES is approved.

116 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

First Generic: No
Approvable/Not Approvable – Minor Deficiency

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

• First Generic?	Yes: ☐	No: ☒
• MR Product?	Yes: ☐	No: ☒
• Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD?	Yes: ☒	No: ☐
• Major Formulation/ Mfg. Process Change?	Yes: ☐	No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – ***No, Information Request***

Review was placed on hold pending DMF review to issue a CR. CR was not issued until today 4-27-2015, the deficiencies are converted to RTC with Information Request as per the current policy.

ANDA 207631

Nilutamide Tablet 150 mg

ANI Pharmaceuticals, Inc

Kadum Al Shareffi, Ph.D
Office of Generic Drug
Division of Chemistry 3
Team 1

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III. List of Deficiencies To Be Communicated 77

A. Deficiencies 78

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: 78

Chemistry Review Data Sheet

1. ANDA: **207631**

2. REVIEW #: **1**

3. REVIEW DATE: **04-27-2014**

4. REVIEWER: **Kadum Al Shareffi, Ph. D**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	06-18-2014
Date acceptance for filling	06-18-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	ANI Pharmaceuticals, Inc (FEI; 2111358)
Address:	210 Main Street West, Baudette MN 56623
Representative:	Ellen Camos / Director, Regulatory Affairs Robert Jamnick / VP Quality and Product Development
Telephone: FAX; Email;	(b) (6) 218.634.3596 888.519.0459/ 218.634.3540 robert.jamnick@anipharmaceuticals.com ellen.camos@anipharmaceuticals.com

*Tel no. for Ellen Camos has changed on 9-25-2014

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Nilutamide Tablet

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: Nilandron® Tablet (Nilutamide)
Innovator company: Covis Pharma SARL (Sanofi Aventis USA)
(NDA # 020169, approved April 30, 1999)

Patent data: There are no unexpired patents for this product
Exclusivity Data: There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __ Rx __ **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5,5-dimethyl-3-(4-nitro-3-(trifluoromethyl) phenyl) imidazolidine-2, 4-dione
Molecular formula: $C_{12}H_{10}F_3N_3O_4$
Molecular weight: 317.25
CAS number: 63612-50-0
Chemical structure:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)		Pending		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Nilandron® (Nilutamide Tablet 150 mg)	NDA 020169 (Covis Pharma SARL / Sanofi Aventis USA)	RLD

18. STATUS

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
Methods Validation		N/A		
Labeling		Pending		
Bioequivalence	Dissolution	Adequate	9-25-2014	Nabeel Babaa
	Bioequivalency	Pending		
Toxicology/Clinical		N/A		
EA		Acceptable	9-23-2014	Kadum Al Shareffi
Radiopharmaceutical		N/A		
Samples Requested		A/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

(b) (4)

Chemistry Review Data Sheet

(b) (4)

[redacted]

Chemistry Review for ANDA 207631

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable. It's recommended a Real Time Communication Information Request be sent to the sponsor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a. Drug Substance

Nilutamide is a microcrystalline, white to practically white powder with a molecular weight of 317.25. Its molecular formula is $C_{12}H_{10}F_3N_3O_4$. It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [<0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

b. Drug Product

(i) Description of drug product

Nilutamide Tablet 150 mg is round biconvex, white to off-white, debossed with "ANI" and "173" on one side and plain on the other side.

(ii) Components of drug product

Active ingredient: Nilutamide

Inactive ingredients: (b) (4) Lactose (b) (4) Povidone, Docusate sodium, (b) (4) and Calcium stearate.

(iii) Manufacturing process of drug product

(b) (4)

(iv) Test method for drug product

The drug product is tested using in-house and USP methods. The HPLC methods for Assay and for related substances are validated or verified as appropriate.

(v) Executed batch and proposed production batches

Strength	Exhibit batch		Intended commercial batch		Scale-up Factor
	Batch size	Batch size (unit)	Batch size	Batch size (unit)	
Nilutamide Tablets 150 mg	(b) (4)				

(vi) Packaging

PROPOSED COMMERCIAL PACKAGING FOR GENERIC NILUTAMIDE TABLETS, 150 MG	
Product	Carton of 3 Blister Cards of 10 Tablets/card
Blister Film	(b) (4)

(vii) Storage conditions

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature] Protect from light. (b) (4)

(viii) Expiration Date

The proposed expiration data for the drug product is (b) (4) for the proposed marketing container/closure system, (b) (4) (b) (4)

The firm provided 12 months of CRT Stability data and 6 months of accelerated stability data for all the packaging. All monitored attributes of the drug product are within the established specifications. No unfavored trend was observed.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS

For use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

HOW SUPPLIED

Nilutamide Tablet 150 mg is supplied in boxes of 30 tablets. (b) (4)

NDC 62559-173-31

ICH Guideline Q3A for Drug substance and Q3B for Drug product of **MDD of 300 mg:**

	ICH Identification threshold	ICH Qualification threshold
Drug substance	0.10%	0.15%

Drug product	0.2%	0.2%

C. Initial and Updated Risk Assessment

(b) (4)

D. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is not approvable. Dissolution is adequate, Bioequivalence is pending. Labeling is pending. EES is pending. This ANDA is not approvable.

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CC: ANDA 207631
ANDA DUP
DIV FILE
Field Copy

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-630/ Kadum Al Shareffi, Ph.D - Reviewer / 10-08-2014/ 04-27-2015
HFD-630/ Guoping Sun, Ph.D., Team Leader
HFD-630/ Dave Gill, PhD - DDD/
HFD-617/ Steve Yang - PM/

F/T by:

V:\Chemistry Division III\Team 31\ANDA REVIEWS\Kadum\207631.R01.doc

TYPE OF LETTER: Minor deficiency

ANDA #	**Product Name and dosage form**	**Review start date**	**Net review days**	(b) (6)
207631	Nilutamide tablet 150 mg	9-16-2014		

CHEMISTRY REVIEW

A. Check List *(once you check a "Yes" from top down, skip the rest afterward)*

• First Generic?	Yes: ☒	No: ☐
• MR Product?	Yes: ☐	No: ☒
• Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD?	Yes: ☐	No: ☒
• Major Formulation/ Mfg. Process Change?	Yes: ☐	No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – *No, IR Letter per Real Time Communication*

Commented [NL1]: This could change based on DMF Please update rest of the document

ANDA 207631

Commented [NL2]: Per Steve, the DMF review should be done by end of this week Please update the DMF and also address few comments made here

Nilutamide Tablets, 150 mg

ANI Pharmaceuticals, Inc.

Kadum Al Shareffi, Ph.D.
Office of Life Cycle Drug Products
Division of IR Products 1
Branch 3

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II. Review of Common Technical Document-Quality (Ctd-Q) Module 1 77

III. List of Deficiencies To Be Communicated 77

A. Deficiencies 78

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: 78

Chemistry Review Data Sheet

1. **ANDA:** **207631**

2. **REVIEW #:** **1**

3. **REVIEW DATE:** **04-27-2015 / 12-04-2015/ 12-8-2015**

4. **REVIEWER:** **Kadum Al Shareffi, Ph. D.**

5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
N/A	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Response to ECD-Labeling	11-10-2015
Quality –Stability Information	09-25-2014
Amendment to the IR letter dated Apr 30, 2015	05-28-2015
Original Submission	06-18-2014

Commented [NL3]: Please include and review information from 1/25/2016 and 3/18/2016

7. **NAME & ADDRESS OF APPLICANT:**

Name:	ANI Pharmaceuticals, Inc (FEI; 2111358)
Address: Applicant's Responsible Official Telephone: Fax; Email;	210 Main Street West, Baudette MN 56623 218-634-3500* 888-519-0459 Ellen Camos, Director of Regulatory Affairs (b) (6) 888.519.0459 ellen.camos@anipharmaceuticals.com
Representative:	David J. Sullivan, Ph.D / Director, Regulatory Affairs Tel: 218-634-3507 Fax: 218-634-3540 Email: david.sullivan@anipharmaceuticals.com

*Tel no. has changed on 11-10-2015

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Nilutamide Tablet

9. **LEGAL BASIS FOR SUBMISSION:**

Innovator Product: Nilandron® Tablet (Nilutamide)

Chemistry Review Data Sheet

Innovator company:	Covis Pharma SARL (Sanofi Aventis USA) (NDA # 020169, approved April 30, 1999)
Patent data:	There are no unexpired patents for this product
Exclusivity Data:	There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2).

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __ Rx __ **OTC**

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

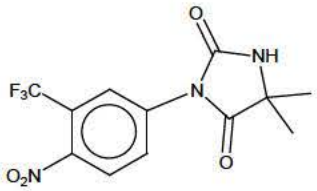
☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:	5, 5-dimethyl-3-(4-nitro-3-(trifluoromethyl) phenyl) imidazolidine-2, 4-dione
Molecular formula:	$C_{12}H_{10}F_3N_3O_4$
Molecular weight:	317.25
CAS number:	63612-50-0
Chemical structure:	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	11-18-2015	Fatima Sequeira
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	IV			4	N/A		

Commented [NL4]: Send an e-mail to RBPM that there is a response from DMF holder that require review

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Nilandron® (Nilutamide Tablet 150 mg)	NDA 020169 (Covis Pharma SARL / Sanofi Aventis USA)	RLD

18. STATUS

Commented [NL5]: Please update the table

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		N/A		
Methods Validation		N/A		
EES		Pending		
Labeling		Pending		
Bioequivalence	Dissolution	Adequate	9-25-2014	Nabeel Babaa
	Bioequivalency	Adequate	10-20-2014	Eunjung Park
Toxicology/Clinical		N/A		
EA		Acceptable	9-23-2015	Kadum Al Shareffi
Radiopharmaceutical		N/A		
Samples Requested		A/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

(b) (4)

[redacted]

Chemistry Review Data Sheet

(b) (4)

Chemistry Review for ANDA 207631

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable. It's recommended an IR Letter under the Real Time Communication.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

a. Drug Substance

Nilutamide is not an official USP monograph, but European Pharmacopeia (EP) has a monograph for Nilutamide. It is a microcrystalline, white to practically white powder with a molecular weight of 317.25. Its molecular formula is $C_{12}H_{10}F_3N_3O_4$. It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [<0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

b. Drug Product

There is no monograph in USP for Nilutamide tablet drug product.

(i) Description of drug product

Nilutamide Tablet 150 mg is round biconvex, white to off-white, debossed with "ANI" and "173" on one side and plain on the other side.

(ii) Components of drug product

Active ingredient: Nilutamide

Inactive ingredients: (b) (4) Lactose (b) (4) Povidone, Docusate sodium, (b) (4) and Calcium stearate.

(iii) Manufacturing process of drug product

(b) (4)

(b) (4)

(iv) Test method for drug product

The drug product is tested using in-house and USP methods. The HPLC methods for Assay and for related substances are validated or verified as appropriate. ANI accepted the recommendation of the DB II specification of the dissolution limit of release of Nilutamide to (b) (4) in the amendment dated 9-25-2014. The dissolution is adequate per DBE.

Commented [NL6]: Thanks for noting this info as part of exe summary

(v) Executed batch and proposed production batches

Strength	Exhibit batch		Intended commercial batch		Scale-up Factor
	Batch size	Batch size (unit)	Batch size	Batch size (unit)	
Nilutamide Tablets 150 mg	(b) (4)				

(vi) Packaging

PROPOSED COMMERCIAL PACKAGING FOR GENERIC NILUTAMIDE TABLETS, 150 MG	
Product	Carton of 3 Blister Cards of 10 Tablets/card
Blister Film	(b) (4)

(vii) Storage conditions

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature] Protect from light. (b) (4)

(viii) Expiration Date

The proposed expiration data for the drug product is (b) (4) for the proposed marketing container/closure system, (b) (4) (b) (4)

The firm provided 12 months of CRT Stability data and 6 months of accelerated stability data for all the packaging. All monitored attributes of the drug product are within the established specifications. No unfavored trend was observed.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS

For use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

HOW SUPPLIED

Executive Summary Section

Nilutamide Tablet 150 mg is supplied in boxes of 30 tablets. (b) (4) .

NDC 62559-173-31

ICH Guideline Q3A for Drug substance and Q3B for Drug product of **MDD of 300 mg:**

	ICH Identification threshold	ICH Qualification threshold
Drug substance	0.10%	0.15%
Drug product	0.2%	0.2%

C. Initial and Updated Risk Assessment

(b) (4)

Executive Summary Section

Alcohol dose dumping	**N/A**	**N/A**	**N/A**	
Other CQAs	**N/A**	**N/A**	**N/A**	

D. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is not acceptable due to DMF inadequacy. Dissolution is Adequate, Bioequivalence is Adequate. Labeling is pending. EES is pending.

73 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Endorsement Block
WO – 75 / Kadum Al Shareffi, Ph.D. - Reviewer / 6-04-2015 / 12-01-2015/12-04-2015/ 12-8-2015
WO – 75 / Laxma Nagavelli, Ph.D., Branch Chief/12/2/2015;12/5/2015;4/13/2016
WO – 75 / Steve Yang - PM/

TYPE OF LETTER: IR letter

ANDA #	Product Name and dosage form	Review start date	Net review days	(b) (6)
207631	Nilutamide tablet 150 mg	9-16-2015	12	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE
ACCEPTABLE OSIS INSPECTION REPORT REVIEW

ANDA No.	207631
Drug Product Name	Nilutamide Tablets
Strength(s)	150 mg
Applicant Name	ANI Pharmaceuticals, Inc.
Original Submission Date(s)	210 Main Street West Baudette, MN 56623
Date of Report	7/6/2016
Reviewer	(b) (6)
Study Number (s)	ANI-NIL.T-07.13-166/127
Study Type (s)	Steady state BE
Strength (s)	150 mg
Clinical Site	King Abdullah University Hospital
Clinical Site Address	PO Box 630001, Irbid 22110, Jordan Tel.: +962 2 7200600- Ext 40508
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**ADEQUATE**

EXECUTIVE SUMMARY

In the bioequivalence (BE) review dated 10/11/2014, the BE section of the application was pending the result of the Office of Study Integrity and Surveillance (OSIS) inspection of the clinical and analytical site.

The OSIS inspection report of the clinical site, King Abdullah University Hospital (PO Box 630001, Irbid 22110, Jordan) and the analytical site (b) (4) was received by the Division of Bioequivalence and found acceptable. The site inspections were requested under the current ANDA on 9/23/2014 and were completed on (b) (4) with an outcome of No Action Indicated (NAI). Given the acceptable inspection of the sites, the OSIS status section of the application is now complete and adequate.

DEFICIENCY COMMENTS:

None

COMMENTS:

No OSIS inspection is pending or necessary for the analytical or clinical site.

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 207631

APPLICANT ANI Pharmaceuticals

DRUG PRODUCT: Nilutamide Tablets, 150 mg

The Division of Bioequivalence II (DBII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Tiffany Pokora

Digitally signed by Tiffany Pokora
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DIVISION OF BIOEQUIVALENCE REVIEW

FULL REVIEW (FISRT GENERIC, STEADY STATE STUDY)

ANDA No.	207631		
Drug Product Name	Nilutamide Tablets		
Strength(s)	150 mg		
Applicant Name	ANI Pharmaceuticals, Inc.		
Address	210 Main Street West Baudette, MN 56623		
Applicant's Point of Contact	Ellen Camos Director, Regulatory Affairs 210 Main Street West Baudette, MN 56623 ellen.camos@anipharmaceuticals.com		
Contact's Telephone Number	(b) (6)		
Contact's Fax Number	888-519-0459		
Original Submission Date(s)	6/18/2014		
Submission Date(s) of Amendment(s) Under Review	09/25/2014: response to ECD/Bioequivalence		
First Generic	Yes		
Reviewer	Eunjung Park, Ph.D.		
Study Number (s)	ANI-NIL.T-07.13-166/127		
Study Type (s)	Steady state BE		
Strength (s)	150 mg		
Clinical Site	King Abdullah University Hospital		
Clinical Site Address	PO Box 630001, Irbid 22110, Jordan Tel.: +962 2 7200600- Ext 40508		
Analytical Site	(b) (4)		
Analytical Site Address			
OSI Status	**Pending**		
OVERALL REVIEW RESULT	**Acceptable**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**N/A**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**Study/Test Type**	**Strength**	**Review Result**
1	**Steady State**	**150 mg**	**adequate**

	Dissolution	**150 mg**	**adequate**

1 EXECUTIVE SUMMARY

This application contains the results of steady state bioequivalence (BE) study comparing a test product, Ani Pharmaceuticals Inc.'s nilutamide tablets, 150 mg to the corresponding reference product, Covis Pharma's Nilandron® (Nilutamide Tablets), 150 mg. Steady State BE study was designed as a single-dose, two-way crossover study in metastatic prostate cancer male patients. The firm's steady state BE studies are acceptable. The results are summarized in the tables below.

Nilutamide, 150 mg Steady State Bioequivalence Study No. ANI-NIL.T-07.13-166/127, N=36 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUCtau (ng·hr/mL)	72353.81	73067.29	0.99	95.84	102.31
Cmaxss (ng/mL)	4160.77	4178.41	1.00	95.49	103.84
Cminss (ng/mL)	2528.97	2519.91	1.00	95.61	105.35

The reviewer performed statistical analysis on cohort 1, 2 and 3 data combined since they meet the following criteria; (1) the clinical study takes place at one site, (2) all study subjects have been recruited from the same enrollment pool, (3) all of the subjects have similar demographics, (4) all enrolled subjects are randomly assigned to treatment groups at study outset.

There is no USP or FDA recommended dissolution method available for this product. The firm developed a new dissolution method and specifications for nilutamide tablets. The firm conducted acceptable dissolution testing. However, the firm's proposed specification of NLT (b) (4) was too liberal to have discriminatory power. The DB II recommended a data-driven specification of NLT (b) (4) (b) (4) The firm accepted above FDA-recommended dissolution specifications as the following[2]:

Apparatus: II (Paddle)
Speed of Rotation: 50 rpm
Medium: 0.54% Sodium Lauryl Sulfate in water
Volume: 900 mL
Temperature: 37.0 ± 0.5 °C
Specification: NLT (b) (4)

The test product is the first generic product; therefore, the inspection history was checked. There is no inspection history for clinical site in Office of Scientific

[1] DARRTS, ANDA 207631, REV-BIOEQ-02 (Dissolution Review), Final Date: 09/12/2014.
[2] DARRTS, ANDA 207631, REV-BIOEQ-02 (Dissolution Review), Final Date: 09/25/2014.

Investigations (OSI) records. The most recent OSI inspection on analytical site was in 2008. The OSI inspections were requested for clinical and analytical sites.

The application is acceptable pending the outcome of inspection of clinical and analytical sites.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Nilutamide Tablets, 150 mg
Reference Product	Nilandron® (Nilutamide Tablets), 150 mg
RLD Manufacturer	Covis Pharma, SARL
NDA No.	020169
RLD Approval Date	04/30/1999
Indication	NILANDRON tablets are indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2).

3.2 PK/PD Information[3,4]

Bioavailability	The drug is rapidly and completely absorbed and that it yields high and persistent plasma concentrations.
Food Effect	Not known
Tmax	Plasma nilutamide levels peaked at 2 hours after ingestion.
Metabolism	The results of a human metabolism study using 14C-radiolabelled tablets show that nilutamide is extensively metabolized and less than 2% of the drug is excreted unchanged in urine after 5 days. Five metabolites have been isolated from human urine. Two metabolites display an asymmetric center, due to oxidation of a methyl group, resulting in the formation of D- and L-isomers. One of the metabolites was shown, in vitro, to possess 25 to 50% of the pharmacological activity of the parent drug, and the D-isomer of the active metabolite showed equal or greater potency compared to the L-isomer. However, the pharmacokinetics and the pharmacodynamics of the metabolites have not been fully investigated.
Excretion	The majority (62%) of orally administered [14C]-nilutamide is eliminated in the urine during the first 120 hours after a single 150-mg dose. Fecal elimination is negligible, ranging from 1.4% to 7% of the dose after 4 to 5 days.
Half-life	38.0 to 59.1 hour (most values between 41 and 49 hours)
Drug Specific Issues (if any)	**Boxed Warning**: *Interstitial Pneumonitis* Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. A small study in Japanese subjects showed that 8 of 47 patients (17%) developed interstitial pneumonitis. Reports of interstitial changes including pulmonary fibrosis that led to hospitalization and death have been reported rarely post-marketing. Symptoms included exertional dyspnea, cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitial changes, and pulmonary function tests revealed a restrictive pattern with decreased DLco. Most cases occurred within the first 3

[3] Label repository; http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=a682f5ef-c79f-419e-94b6-b1a84b7b6651

[4] Enterprise Search: Clinical Pharmacology and Biopharmaceutics Review of NDA 20-169. (submission date: 03/07, 07/12,09/02, 09/27, 10/24, 12/05/1994 and 01/18/1995)

	months of treatment with NILANDRON, and most reversed with discontinuation of therapy. A routine chest X-ray should be performed prior to initiating treatment with NILANDRON. Baseline pulmonary function tests may be considered. Patients should be instructed to report any new or worsening shortness of breath that they experience while on NILANDRON. If symptoms occur, NILANDRON should be immediately discontinued until it can be determined if the symptoms are drug related.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1

1.	**Type of study:**	Steady-State
	Design:	Steady state, two-way crossover or parallel *in-vivo* study
	Strength:	150 mg
	Subjects:	Patients who are already receiving the drug at a dose of 150 mg once a day as their individual therapy and continuing on the same dose for both periods of the crossover study.
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Nilutamide in plasma
Bioequivalence based on:	(90% CI) Nilutamide
Waiver request of in-vivo testing:	Not Applicable
Source of most recent recommendations:	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081328.htm Original draft guidance published in 2009 which recommended the fasting and fed study. The guidance finalized in 2011 and recommends only a steady state in vivo study. The control document that supports this final guidance was not found in the control database but protocol review of 07-071 addendum (07071p1107Addendem)[5] recommends following based on the reviews of Clinical Review Team and Division of Pulmonary and Allergy Products considering patient safety: *The steady-state should be conducted in patients who are receiving the 150 mg once a day treatment to ensure the patients continue on their same dose for both periods of the crossover study.*

[5] V:\FIRMSNZ\ROXANE\PROTOCOLS

Summary of OGD or DBE History (for details, see Appendix Error! Reference source not found.**):**	This is the first generic of Nilutamide Tablets. Pending ANDAs: none as of September 5, 2014 Controls: 08-0396 (b) (4) 09-0427 11-0132 13-0198 Protocols: 07-071 (b) (4) 07-074 10-017

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	Yes	1
In vitro dissolution	Yes	1
Waiver requests	No	0
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.2 (Clinical Report: APPENDIX 16.2)
Analyte	Nilutamide
Internal standard (IS)	Nilutamide-d6
Method description	(b) (4)
Limit of quantitation	50.000 ng/mL
Average recovery of drug (%)	83.96%
Average recovery of IS (%)	83.96%
Standard curve concentrations (units/mL)	50.000-10000.000 ng/mL
QC concentrations (units/mL)	LLOQ: 500.00 ng/mL QCLow: 1500.00 ng/mL QCmed : 40000.00 ng/mL QCHigh: 80000.00 ng/mL
QC Intraday* precision range (%)	Day1: LLOQ-2.93, QClow-3.52, QCmed-2.19, QChigh-0.86 Day2: LLOQ-6.05, QClow-4.82, QCmed-2.14, QChigh-1.78 Day3: LLOQ-5.46, QClow-4.79, QCmed-1.35, QChigh-3.1
QC Intraday* accuracy range (%)	Day1: LLOQ-94.9, QClow-99.2, QCmed-98.9, QChigh-95.2 Day2: LLOQ-99.1, QClow-98.3, QCmed-99.7, QChigh-98.0 Day3: LLOQ-98.4, QClow-93.1, QCmed-94.1, QChigh-91.6
QC Interday* precision range (%)	LLOQ-5.40, QClow-5.01, QCmed-3.10, QChigh-3.58
QC Interday* accuracy range (%)	LLOQ-97.8, QClow-97.2, QCmed-98.1, QChigh-95.7
Bench-top stability (hrs)	6 hr at RT
Stock stability (days)	3 days at RT and 20 days at 2-8 °C
Processed stability (hrs)	32 hr 5 min at auto-sampler temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	Analyte : 207 days at -70 °C
Dilution integrity	Samples above the linear range (up to three times higher) can be diluted to the linear range and can be precisely determined and reported.
Selectivity	No peak considered as significant interfering with Nilutamide and/ or Nilutamide-d6 was found.

*Intra-batch and inter-batch data

SOPs submitted	REPEAT ANALYSIS FOR UNKNOWN SAMPLES (BAN-1102)
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation: Adequate

The firm submitted accuracy and precision results of six sets quality control samples at each concentration level (low, medium, and high concentrations in addition to the LLOQ) for Day 1 and 3 and twelve set of Day 2, which were extracted and analyzed with the same calibration curve to verify the intra-assay accuracy and precision for each day separately. Eventually they submitted three sets of intra-day accuracy and precision. They used the same data to generate inter-day accuracy and precision. It is acceptable.

The firm submitted a SOP for repeat analysis for unknown samples but did not submit SOPs for analytical method and validation in the original submission. After ECD issued, the firm provided following SOPs in the amendment[6]: Bioanalytical Method Development (b) (4) Bioanalytical Method Validation (b) (4) Standard Practices for Chromatographic Analysis (b) (4) Handling of Standard Curve and QC Results (b) (4) and incurred sample analysis (b) (4) .[7]

The firm did not submit raw numerical HPLC data for all subjects in the original submission but later provided the raw data in this amendment.

LTSS was reported as 207 days at -70°C in the bio-summary table but not in the validation report. The firm clarified the validation report was not updated inadvertently and submitted the updated HPLC-MS Bioanalytical Method Validation Report (Rev01).

Overall, the pre-study analytical validation is adequate.

[6] DARRTS, ANDA 207631, Supporting document 3, response to ECD/Bioequivalence, submit date: 09/25/2014

[7] Module 5.3.1.2. Comparative BA and BE study reports/SOPs

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					$C_{max(ss)}$ ng/mL	$C_{min(ss)}$ ng/mL	AUC_{0-tau} (ng*hr/ml)	Fluctuation (%)	Swing	T_{max} hr	
Study# ANI-NIL.T-07.13-166/127	Multicenter, Randomized, Two-Period Crossover, Open label, Laboratory-Blind Steady State Bioequivalence Study for Nilutamide 150 mg Tablets (Test Product- ANI Pharmaceuticals, Inc., USA)- and Nilandron® 150 mg Tablets (Reference Product- Sanofi Aventis, USA) after a single daily dose of 150 mg Nilutamide to metastatic prostate cancer male patients	Randomized Multiple dose Steady State Crossover	Nilutamide 150 mg Tablets p.o. [Batch # C-0404-31] Nilandron® 150 mg Tablets p.o. [Batch # 2AL3A]	36 subjects completed Male subjects with Metastatic Prostate Cancer Age (Mean): 68± 6.6 yrs (56-81 yrs)	Test 4245.732 ±826.3440 CV 19.46% Reference 4248.888 ±698.6994 CV 16.44%	Test 2597.309 ±573.0261 CV 22.06% Reference 2571.232 ±492.3373 CV 19.15%	Test 73900.753 ±14613.9664 CV 19.78% Reference 74237.166 ±12372.3155 CV 16.67%	Test 54.50 ±16.688 CV 30.62% Reference 55.30 ± 16.211 CV 29.32%	Test 0.66 ±0.236 CV 35.77% Reference 0.67 ± 0.213 CV 31.65%	Test 2.61 ±1.997 Range 0.50-12.00 CV 76.47% Reference 2.57 ±1.116 Range: 0.50-5.00 CV 43.43%	Module 5.3.1.2

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Nilutamide (n=36) 150 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ANI-NIL.T-07.13-166/127)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUCtau (hr *ng/ml)	72353.81	73067.29	0.99	95.84	102.31
Cmaxss (ng/ml)	4160.77	4178.41	1.00	95.49	103.84
Cminss (ng/ml)	2528.97	2519.91	1.00	95.61	105.35

Table 3. Reanalysis of Study Samples

Study No. ANI-NIL.T-07.13-166/127 Steady State BE study								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays***	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reason: Technical Error	7.0	5.0	0.93	0.66	7.0	5.0	0.93	0.66
Total	7.0	5.0	0.93	0.66	7.0	5.0	0.93	0.66

Did use of recalculated plasma concentration data change study outcome? N/A

There are 12 samples repeated due to technical errors such as preparation error and internal standard area.
The reviewer did not recalculate plasma concentration since there was no PK repeat.

BEFORE REPEAT			AFTER REPEAT					
SAMPLE ID	ORIGINAL CONCENTRATION (NG/ ML)	REASON FOR REPEAT	DATE	CONCENTRATION (NG /ML)	DILUTION FACTOR*	REPORTED CONCENTRATION (NG/ML)	REPORTING JUSTIFICATION	COMMENTS
11-II-Zero (day 17)	866.860	TE	05/May/2014	1682.706 1583.105 1679.631	1	1648.481	2	IS area >170 % of mean IS area of the calibration curve.
15-II-1.00	3924.450	TE	05/May/2014	4068.667 4061.920 3702.893	1	3944.493	2	IS area < 30 % of mean IS area of the calibration curve.
16-I-Pre-dose (day17)	N/A	TE	05/May/2014	0.000 0.000 0.000	1	0.000	2	LC Error.
16-I-Pre-dose (day19)	3509.418	TE	05/May/2014	0.000 0.000 0.000	1	0.000	2	Preparation Error (Internal Standard added by mistake); **IS should not be added to blank samples.**
16-I-Zero (day17)	N/A	TE	05/May/2014	2962.905 2912.524 2950.184	1	2941.871	2	Preparation Error (No Internal Standard added by mistake); **IS should be added to zero samples.**
37-II-8.00	6234.991	TE	05/May/2014	2465.050 2657.388 2585.755	1	2569.398	2	IS area <30 % of mean IS area of the calibration curve.
37-I-12.00	6704.555	TE	05/May/2014	2430.088 2401.648 2427.096	1	2419.611	2	IS area <30 % of mean IS area of the calibration curve
37-II-12.00	7012.039	TE	05/May/2014	2380.495 2601.311 2546.953	1	2509.586	2	IS area <30 % of mean IS area of the calibration curve
37-I-24.00	5653.912	TE	05/May/2014	2161.012 2223.405 2137.455	1	2173.957	2	IS area <30 % of mean IS area of the calibration curve
37-II-24.00	5687.509	TE	05/May/2014	3098.458 2975.187 2898.440	1	2990.695	2	IS area <30 % of mean IS area of the calibration curve

41-II-3.00	N/A	TE	05/May/2014	5412.473 6113.276 5554.571	1	5693.440	2	Preparation Error (No Internal Standard added by mistake); **IS should added to Post dose Samples**.
34-II-Zero (day 19)	3193.424	TE	05/May/2014	3396.489 3512.450 3223.430	1	3377.456	2	IS area <30 % of mean IS area of the calibration curve

Comments from the Reviewer: Acceptable

3.7 Formulation

Location in appendix	Section 4.2, Page 33
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS, ANDA 207631, REV-BIOEQ-02 (Dissolution Review), Final Date: 09/12/2014 and 9/25/14
Source of Method (USP, FDA or Firm)	Firm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
DBE-recommended specifications	NLT (b) (4)
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

F2 metric, biostudy strengths Test vs Reference	
Biostudy Strength	**QC medium**
150 mg	67.61

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

3.10 OSI Inspection Status

The test product is the first generic product; therefore, the inspection history was checked. There is no inspection history for clinical site, King Abdullah University Hospital, Jordan in OSI records. The most recent OSI inspection on analytical site, (b) (4) OSI inspections for clinical and analytical sites were requested on September 23, 2014.

3.11 Deficiency Comments

None

3.12 Recommendations

1. The Division of Bioequivalence II accepts the steady state BE study (ANI-NIL.T-07.13-166/127) conducted by the Ani Pharmaceuticals on its nilutamide tablets, 150 mg (lot # C-0404-31) comparing it to Covis Pharma's Nilandron® Tablets 150 mg (lot # 2AL3A).

2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.54% Sodium Lauryl Sulfate in water at 37°C ± 0.5°C using USP apparatus II at 50 rpm. The test product should meet the following specification:

   NLT (b) (4)

   The Division of Bioequivalence II deems the test product nilutamide tablets, manufactured by Ani Pharmaceuticals, to be bioequivalent to the reference product, Nilandron® Tablets 150 mg, manufactured by Covis Pharma, SARL.

3.13 Comments for Other OGD Disciplines

Discipline	Comment
RPM and CSO	Dissolution was reviewed in DARRTS; ANDA 207631, REV-BIOEQ-02 (Dissolution Review), Final Date: 09/12/2014 and 9/25/2014. Please refer to the reviews for dissolution results.
OSI	Inspections for clinical and analytical site were requested.

[8] DARRTS, ANDA 207631, FRM-CONSULT-09(Biopharmaceutical Inspections Request), Submit Date: 09/23/2014

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Steady State in vivo Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	ANI-NIL.T-07.13-166/127
Study Title	Multicenter*, Randomized, Two-Period Crossover, Open label, Laboratory-Blind Steady State Bioequivalence Study for Nilutamide 150 mg Tablets (Test Product- ANI Pharmaceuticals, Inc., USA)- and Nilandron® 150 mg Tablets (Reference Product- Sanofi Aventis, USA) after a single daily dose of 150 mg Nilutamide to metastatic prostate cancer male patients
Clinical Site (Name & Address)	King Abdullah University Hospital, PO Box 630001, Irbid 22110, Jordan Tel.: +962 2 7200600- Ext 40508
Principal Investigator	Dr. Rami Al-Azab, MD E-mail: (b) (6)
Dosing Dates	Cohort 1: 23/Nov/2013 – 31/Dec/2013 Cohort 2: 31/Jan2014 - 10/Mar/2014 Cohort 3: 24/Mar/2014 – 01/May/2014
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	25/Apr/2014-05/May/2014
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	(a) 151 days (b) -70 °C

*Note for study design:
The study was conducted in a single center not multicenter.[9]

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Nilutamide Tablets	Nilandron® (Nilutamide Tablets)
Manufacturer	ANI Pharmaceuticals, Inc.	Sanofi Aventis- USA (Covis Pharma SARL)

[9] Module 5.3.1.2. Study report body page 31.

Batch/Lot No.	C-0404-31	2AL3A
Manufacture Date	April 9, 2013	N/A
Expiration Date	03/2015	03/2015
Strength	150 mg	150 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97.6%	100.0%
Content Uniformity (mean, %CV)	97.6%	100.0%
Dose Administered	150 mg/ day for 19 days	150 mg/ day for 19 days
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Number of subject in study =42 Number of subject completed = 36
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	0
Randomization Scheme	AB: 2, 4, 7, 9, 10, 13, 16, 18, 23, 24, 25, 27, 28, 29, 30, 31, 33, 34, 37, 40, 41 BA: 1, 3, 5, 6, 8, 11, 12, 14, 15, 17, 19, 20, 21, 22, 26, 32, 35, 36, 38, 39, 42
Blood Sampling Times	pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 hours
Blood Volume Collected/Sample	8 mL

Blood Sample Processing/Storage	Cannula was inserted in the subject's arm before withdrawal of the pre-dose sample on day 19 up to the 24 hour post day 19 dose sample. The pre-dose sample was withdrawn and the cannula was then flushed with heparin (0.5ml, 1% heparin solution) to prevent cannula clogging. The first 0.5 mL withdrawn in each of the subsequent samples was discarded due to the heparinized solution. After each sampling the cannula was flushed with heparin. Blood samples were collected at the times specified previously in a pre-labeled lithium heparinated 10 mL tubes. They were centrifuged within one hour from the collection at 4000 rpm for 5 minutes at room temperature (samples were kept in wet ice until centrifugation). The resulting plasma was transferred and divided directly into two labeled plastic cryo-polypropylen tubes. These samples were finally stored at a temperature -70°C freezer.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	N/A
Length of Confinement	N/A
Safety Monitoring	**Day 10 (period I and II):** subjects went through an ECG examination, hepatic functions, and fasting blood sugar. Vital signs were examined before dosing. KFT (creatinine, potassium, chloride, sodium, and urea), electrolytes, serum calcium and magnesium were examined. **Day 20 (period I only):** vital signs and fasting blood sugar measurements were examined. **Final examination (Day 20 of period II):** physical examination, vital signs measurement, ECG and clinical laboratory tests, clinical chemistry, fasting blood sugar, serum Calcium, and Magnesium, and urinalysis were performed. Chest X-ray and full pulmonary function test were also performed to rule out any pulmonary toxicity caused by the drug. Subjects withdrawn from the study had a final examination depending on their withdrawing circumstances and as deemed necessary by the Principal/Clinical co- investigator.

Comments on Study Design: Acceptable

The patients were dosed from day 1 to day 19 once a day and measured three pre-dose concentrations on day 16, 17, and 18. On days 1, 10 and 19 of both periods, subjects received the designated drug under fasting conditions at least for 10 hrs before the dosing time, and on the remaining days (no. 2-9, and 11-18) in both periods, fasting was not mandatory before dosing.

Each period consisted of 20 days:
Day 1- 19: Dosing on each day.
Days 16, 17 and 18: pre-dose sample

Day 19: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 hours samples.
Day 20 (Period I): 24 hours post- day 19 dose sample; and dosing for period II starts
Day 20 (Period II): 24 hours post- day 19 dose sample; and final examination.
Study subjects received either the test or reference product in each period according to the randomization scheme. There is no wash out period since the study design is steady state BE study.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. ANI-NIL.T-07.13-166/127			
		Treatment Groups	
		Test Product N = 36	Reference Product N = 36
Age (years)	Mean ± SD	68±6.6	68±6.6
	Range	56-81	56-81
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	0 (0%)	0 (0%)
	41 – 64	12 (33.33%)	12 (33.33%)
	65 – 75	19 (52.77%)	19 (52.77%)
	> 75	5 (13.89%)	5 (13.89%)
Sex	Male	36 (100%)	36 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	0 (0%)	0 (0%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	36 (100%)	36 (100%)
BMI	Mean ± SD	29.49±5.075	29.49±5.075
	Range	21.79-44.58	21.79-44.5868
Other Factors		N/A	N/A

Table 1. Demographic Characteristics of study population- Cohort 1

Parameter	*Age (Years)*	*Height (m)*	*Weight (Kg)*	*BMI (Kg/m^2)*
N	12	12	12	12
Mean	65	1.68	88	30.94
SD	6.1	0.043	15.6	4.772
Range	56-74	1.6-1.74	59-116	21.93-38.31

Table 2. Demographic Characteristics of study population- Cohort 2

Parameter	*Age (Years)*	*Height (m)*	*Weight (Kg)*	*BMI (Kg/m^2)*
N	11	11	11	11
Mean	72	1.68	81	28.62
SD	4.5	0.081	19.3	5.860
Range	62-77	1.51-1.80	60-135	23.71-44.58

Table 3. Demographic Characteristics of study population- Cohort 3

Parameter	*Age (Years)*	*Height (m)*	*Weight (Kg)*	*BMI (Kg/m^2)*
N	19	19	19	19
Mean	69	1.68	83	29.13
SD	6.9	0.074	16.5	4.720
Range	59-81	1.56-1.86	64-133	21.79-38.44

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. ANI-NIL.T-07.13-166/127				
Subject ID	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Abnormal Lab Results (HB Low,PCV Low, RBC Low,MCH Low,MCHC Low)	N/A	No	N/A
	Abnormal Lab Results (serum creatinine high, serum urea high)	N/A	No	N/A
	Medical Reason:-Serious Adverse event:-Chest pain preceding headache and hypertension	I	No	N/A
	Didn't meet study protocol selection criteria (Age>85 years old)	N/A	No	N/A
	Personal Reason	I	No	N/A
	Personal Reason	I	No	N/A
	Personal Reason	I	No	N/A
	Medical Reason:- Adverse events:-(Headache, Dizziness, Cough, Fever)	I	No	N/A
	Personal Reason	I	No	N/A

Notes for dropouts:
The three **unassigned** subjects were listed in the above dropout table but these subjects without subject ID were not included in the study at all. There are two dropouts due to adverse events and four dropouts due to personal reasons. The subjects were not replaced.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. ANI-NIL.T-07.13-166/127	
	Test	Reference
Flu	1 (2.78%)	0 (0%)
Fever	3 (8.33%)	2 (5.56%)
Oral Aphthous ulcer	1 (2.78%)	0 (0%)
Sore Throat	4 (11.11%)	2 (5.56%)
Decreased visual acuity	11 (30.56%)	9 (25%)
Headache	4 (11.11%)	2 (5.56%)
Throat Irritation	1 (2.78%)	0 (0%)
Throat Congestion and Irritation	1 (2.78%)	0 (0%)
Hematuria	1 (2.78%)	0 (0%)
Hypertension	1 (2.78%)	1 (2.78%)
Chest pain	1 (2.78%)	0 (0%)
Finger pain	0 (0%)	1 (2.78%)
Malena	0 (0%)	1 (2.78%)
Anxiety	0 (0%)	1 (2.78%)
Fatigue	1 (2.78%)	3 (8.33%)
Dark urine	0 (0%)	1 (2.78%)
Burning Micturition	2 (5.56%)	2 (5.56%)
Constipation	0 (0%)	1 (2.78%)
Skin Irritation	0 (0%)	1 (2.78%)
Dry Mouth	0 (0%)	1 (2.78%)
Dizziness	3 (8.33%)	2 (5.56%)
Sweating	2 (5.56%)	1 (2.78%)
Difficulty in Micturition	1 (2.78%)	0 (0%)
Productive Cough	1 (2.78%)	1 (2.78%)
Epistaxis	1 (2.78%)	0 (0%)
Dyspnea	0 (0%)	1 (2.78%)

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. ANI-NIL.T-07.13-166/127	
	Test	Reference
Abdomenal Gases*[10]	0 (0%)	0 (0%)
Numbness	0 (0%)	1 (2.78%)
Hand Swelling	0 (0%)	1 (2.78%)
Muscle Spasm	0 (0%)	1 (2.78%)
Light urine colouration	0 (0%)	1 (2.78%)
Nausea	0 (0%)	1 (2.78%)
Hot Flushes/Flushing	4 (11.11%)	7 (21.21%)
Acute Renal Failure	0 (0%)	1 (2.78%)
Chest Infection	0 (0%)	1 (2.78%)
Shivering	0 (0%)	1 (2.78%)
Drowsiness	0 (0%)	1 (2.78%)
Foot/Thigh pain	2 (5.56%)	0 (0%)
Rise of Random Blood Sugar	0 (0%)	1 (2.78%)
Enlarged Prostate	0 (0%)	1 (2.78%)
Bones Pain	1 (2.78%)	0 (0%)
Sexual Activity Weakness	1 (2.78%)	0 (0%)
Heart Burn	1 (2.78%)	1 (2.78%)
Diarrhea	1 (2.78%)	0 (0%)
Dyspepsia	0 (0%)	1 (2.78%)

Note for adverse events:
There are 10 subjects and 20 subjects experienced adverse events for test and reference product, respectively. The subjects (b) (6) (test), (b) (6) (test), and (b) (6) (reference) were suffered from a serious adverse events but completely resolved. Mostly adverse events are possibly or probably related to treatment and there is no adverse event definitely related to treatment. Most frequent adverse event is decreased visual acuity for both test and reference product. No subject reported experiencing emesis during the study. There is no death reported.

[10] Subject Randomization no. (b) (6) suffered from the abdominal gases before being administered the first dose of
the first period.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. ANI-NIL.T-07.13-166/127		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Deviation in drug administration time	(b) (6)	
Deviation in sample collection		
Deviation in protocol procedures		

Note on protocol deviations:

1. Deviation in drug administration time:
   a. Due to bad weather, subjects were late to come to clinical site (subject ID, (b) (6) at day 16 (pre-dose).
   b. Due to subject's prostate surgery, the subject (b) (6) had been administered the study drug one hour early at Day 16 (pre-dose).
   c. Due to delay in withdrawing the PK sample of period I, the subject (b) (6) had been administered the study drug 12 minutes later than determined time at day 19 (24 hr).
2. Deviation in sample collection:
   a. There are sampling time deviations which are less than 5% difference from nominal sampling time (please see below table).

Study Code: ANI-NIL.T-07.13-166/127 Period II

Acceptable Deviation from theoretical time: Day 16 – Day 18 (blood sampling should 5 minutes prior to dosing)

Subject No.	Dosing Time (hr)	Blood Sampling Time (hr)	Deviation* (hr)	
			Delay	Early
(b) (6) day 16)	09:14	09:08	N/A	00:01
day 18)	09:28	09:22	N/A	00:01
day 18)	09:30	09:24	N/A	00:01
day 18)	09:32	09:26	N/A	00:01
day 18)	09:34	09:28	N/A	00:01

Acceptable deviation from theoretical time: BK-24.00 ± 2 minutes

Subject No.	Theoretical Time (hr)	Actual Time (hr)	Deviation* (hr)	
			Delay	Early
(b) (6) (day 19) (1.50 hr)	10:38	10:39	*00:01	N/A
(day 19) (1.50 hr)	10:40	10:41	*00:01	N/A
day 19) (24.00 hr)	09:32	09:34	*00:02	N/A

Study Code: ANI-NIL.T-07.13-166/127 Period I Acceptable Deviation from theoretical time: Day 16 – Day 18 (blood sampling should be 5 minutes prior to dosing)				
Subject No.	Dosing Time (hr)	Sample Collection Time (hr)	Deviation* (hr)	
			Delay	Early
(b) (6) (day 16)	09:11	09:05	N/A	00:01

Acceptable deviation from theoretical time: BK-24.00 ± 2 minutes				
Subject No.	Theoretical Time (hr)	Actual Time (hr)	Deviation* (hr)	
			Delay	Early
(b) (6) (day 19) (24.00)	09:06	09:19	00:13	N/A

3. Deviation in protocol procedures:
    a. Subject (b) (6) (period I day 16, pre-dose) was double dosed (300 mg) by subject's misunderstanding on day 16. The principal investigator and technical director concluded this deviation should have no effect on the study outcome or the subject safety. Maximum daily dose of nilutamide is 300 mg.
    b. The aPTT test of Subject (b) (6) was not performed inadvertently but it was normal at the subject's next visit.
    c. Subject (b) (6) did not take the dose on day 6 (pre-dose) inadvertently.

Comments on Dropouts/Adverse Events/Protocol Deviations: Acceptable

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Analyte 1								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	50.000	100.000	200.000	500.000	2000.000	5000.000	7500.000	10000.000
Inter day Precision (%CV)	6.39	6.55	9.78	8.44	9.00	7.17	8.51	9.63
Inter day Accuracy (%Actual)	98.43	93.95	87.54	88.04	87.91	93.11	90.92	88.63
Linearity	0.9986							
Linearity Range (ng/mL)	50.00-10000.00							
Sensitivity/LOQ (ng/mL)	50.00							

Parameter	**Quality Control Samples**		
Concentration (ng/mL)	150.00	4000.00	8000.00
Inter day Precision (%CV)	5.01	3.10	3.58
Inter day Accuracy (%Actual)	97.20	98.09	95.37

Comments on Study Assay Validation: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Randomly (b) (6)

Comments on Chromatograms: Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	**Effective Date of SOP**	**SOP Title**
(b) (4)		**REPEAT ANALYSIS FOR UNKNOWN SAMPLES**

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

Fasting Bioequivalence Study, Study No.									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUCtau (ng*hr/mL)	73900	19.8	36124.8	100495.2	74235	16.7	45409.4	95813.0	0.996
Cmaxss (ng/mL)	4245.7	19.5	2172.7	5719.1	4248.9	16.44	2614.4	5693.4	0.999
Cminss (ng/mL)	2597.3	22.1	1153.1	4187.3	2571.2	19.1	1508.4	3514.3	1.010
Swing	0.659	35.8	0.225	1.378	0.674	31.7	0.313	1.366	0.978
FLUC (%)	54	31.5	21.0	101.4	55	29.1	27.8	113.9	0.982
Tmax (hr)	2.61	76.6	0.5	12	2.57	43.6	0.5	5	1.016

* Tmax values are presented as median, range

Note for Tmax: The reviewer considers the 30 minutes (one sampling time difference) difference of Tmax between the test and reference product is acceptable.

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated by WinNonlin® Version 6.3.

Nilutamide (n=36) Dose (# 150 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ANI-NIL.T-07.13-166/127)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC0-tau	72353.81	73067.29	99.02353	95.841	102.312
Cmaxss	4160.771	4178.41	99.57785	95.602	103.719
Cminss	2528.975	2519.914	100.3596	95.732	105.210

Table 16A. Geometric Means and 90% Confidence Intervals - Reviewer Calculated by Phoenix 64 Software.

Nilutamide (n=36) Dose (# 150 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ANI-NIL.T-07.13-166/127)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUCtau (hr *ng/ml)	72353.81	73067.29	99.02353	95.841	102.312
Cmaxss (ng/ml)	4160.771	4178.41	99.57785	95.493	103.838
Cminss (ng/ml)	2528.975	2519.914	100.3596	95.606	105.350

Note for analysis:

The reviewer reanalyzed the firm's concentration and PK data using NCA (non-compartmental analysis) and the result is same with the firm's analysis. The range of the difference of 90% CI between firm and reviewer is ~0.1. The reviewer considers this is not a significant difference since the 90% CI are relatively tight and fell within acceptable BE Criteria.

Table 17B. Geometric Means and 90% Confidence Intervals - Reviewer Calculated by SAS

Nilutamide (n=36) Dose (# 150 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. ANI-NIL.T-07.13-166/127)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUCtau (hr *ng/ml)	72353.81	73067.29	0.99	95.84	102.31
Cmaxss (ng/ml)	4160.77	4178.41	1.00	95.49	103.84
Cminss (ng/ml)	2528.97	2519.91	1.00	95.61	105.35

Note for SAS analysis:
The reviewer used the same concentration data without any change. The SAS results are same with Phoenix data.

Table 18. Additional Study Information, Fasting Study No. ANI-NIL.T-07.13-166/127

Root mean square error, AUC0-t	0.0818	
Root mean square error, Cmaxss	0.1049	
Root mean square error, Cminss	0.1216	
	Test	**Reference**
Kel determined for how many subjects?	36	36
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		

measurable drug concentrations at 0 hr	N/A	N/A
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm's statistical analysis indicates the ANOVA analysis of nilutamide demonstrated that the cohort effect for all bioequivalence metrics did not influence the outcome of the study. The reviewer also confirmed that the cohort effect did not influence the Cmax, Cmin and AUCtau. The reviewer's ANOVA analysis data in treatment, period, sequence or cohort effect for Cmax, Cmin and AUCtau (i.e. $p \geq 0.1$) is listed in the below table. ANOVA did not detect statistical significance in treatment, period, sequence or cohort effects for in reviewer's analysis.

P values	Cmax,ss	Cmin,ss	AUCtau
Period	0.1367	0.9946	0.5374
Sequence	0.3544	0.7040	0.8441
Treatment	0.9861	0.8365	0.9163
Cohort	0.9333	0.5460	0.3843

2. The reviewer performed statistical analysis on cohort 1, 2 and 3 data combined since they meet the following criteria: 1) the clinical study takes place at one site (King Abdullah University Hospital), 2) all study subjects have been recruited from the same enrollment pool, 3) all of the subjects have similar demographics (age 65- 72 years old, BMI 28.62 – 30.94 Kg/m^2, section 4.1.1.2), and 4) all enrolled subjects are randomly assigned to treatment groups at study outset.

Table 1. Study Timelines

Sponsor Protocol Approval Original: 19/Apr/2013 Amendment 01: 24/July/2013 Amendment 02: 03/Oct/2013	**IRB Approval:** Original: 17/June/2013 Amendment 01: 22/Aug/2013 Amendment 02: 21/Oct/2013	**JFDA Approval** Original: 15/July/2013 Amendment 01: 05/Sep/2013 Amendment 02: 27/Oct/2013	**Screening (Cohort 1)** Cohort 1: 19-20/Nov/2013	**Screening (Cohort 2)** Cohort 2: 27/Jan/2014	**Screening (Cohort 3)** Cohort 3: 18-19/Mar/2014

Cohort 1			
Enrollment Date	**Period I Date**	**Period II Date**	**Last blood sample**
22/Nov/2013	23/Nov/2013-12/Dec/2013	12/Dec/2013-31/Dec/2013	31/Dec/2013
Cohort 2			
Enrollment Date	**Period I Date**	**Period II Date**	**Last blood sample**
30/Jan/2014	31/Jan/2014-19/Feb/2014	19/Feb/2014-10/Mar/2014	10/Mar/2014
Cohort 3			
Enrollment Date	**Period I Date**	**Period II Date**	**Last blood sample**
23/Mar/2014	24/Mar/2014-12/Apr/2014	12/Apr/2014-01/May/2014	01/May/2014

Last blood sample Date	**Bio-analysis**	**PK analysis & Reporting**
01/May/2014	25/Apr/2014-05/May/2014	05/May/2014- 07/June/2014

3. The firm's statistical analysis was conducted using the WinNonlin® computer program version 6.3 not SAS program. Therefore, the firm did not submit SAS output. The reviewer analyzed the PK data using Phoenix program to confirm the firm's analysis result. The difference between firm's and reviewer's data is negligible. In addition, the reviewer reanalyzed data using SAS and the results are same with Phoenix analysis.

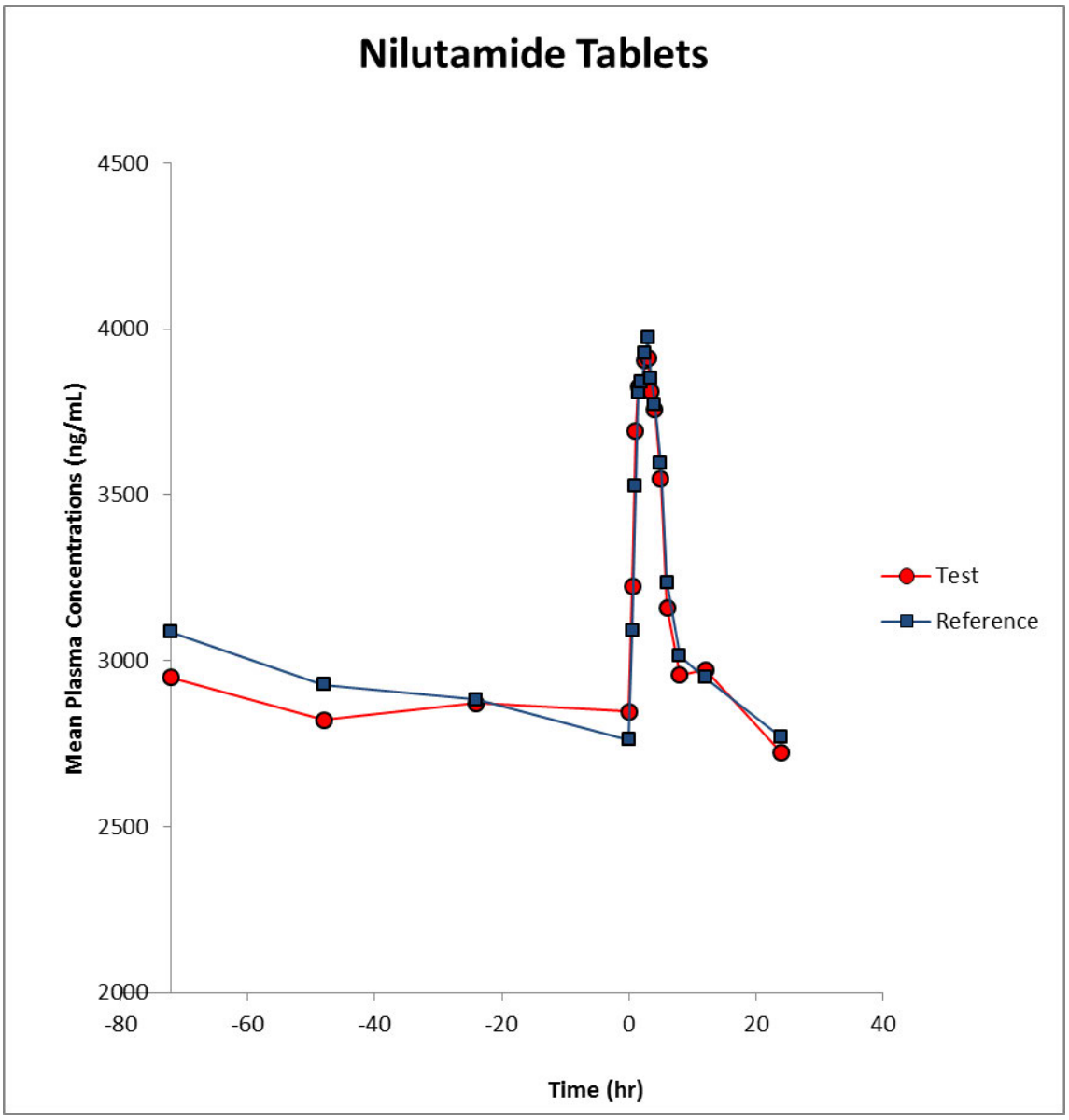
4. The 90% CIs for the geometric least squares means of AUCτ (0-24), lnCminss and lnCmaxss of the test product, nilutamide tablets, 150 mg, calculated by the reviewer match the firm's data and meet the BE limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Nilutamide					
Time (hr)	Test (n=36)		Reference (n=36)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	2846.19	21.91034	2762.55	19.59422	1.03
0.5	3224.38	21.53158	3092.31	22.87125	1.04
1	3693.82	22.26909	3526.46	22.04562	1.05
1.5	3825.19	19.85914	3809.57	16.55804	1.00
2	3814.78	18.84407	3839.42	16.15609	0.99
2.5	3906.63	20.74013	3926.02	16.33817	1.00
3	3913.26	20.61069	3973.19	18.06256	0.98
3.5	3810.29	20.85169	3850.67	17.09495	0.99
4	3759.08	21.0078	3770.86	17.86118	1.00
5	3547.53	21.1395	3594.22	17.54595	0.99
6	3159.4	19.793	3236.55	18.00868	0.98
8	2956.94	20.1925	3014.73	17.85599	0.98
12	2973.46	23.37916	2949.66	18.68859	1.01
24	2721.77	22.51513	2769.43	19.99112	0.98

Figure 1. Mean Plasma Concentrations, Single-Dose Steady State Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Tablets	Amount (%) / Tablet
[redacted]	[redacted]	[redacted]
Nilutamide	150.0	[redacted]
[redacted]	[redacted]	[redacted]
Lactose [redacted] NF [redacted]	[redacted]	[redacted]
Povidone, USP [redacted]	[redacted]	[redacted]
Docusate Sodium, USP [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Talc, USP	[redacted]	[redacted]
Calcium Stearate, NF	[redacted]	[redacted]
Total	**400.0 mg**	[redacted]

Note for formulation:
The proposed test product and RLD are both oral dosage form containing the same active ingredient. A comparison of the test product to the RLD is provided in the table below.
[redacted]

[11] Quantity sufficient

INACTIVE INGREDIENT COMPARISON		
PROPOSED ANDA DRUG PRODUCT	REFERENCE LISTED DRUG	INACTIVE INGREDIENT FUNCTION
(b) (4)	Corn Starch	(b) (4)
Lactose (b) (4) NF (b) (4)	Lactose	
Povidone, USP	Povidone	
Docusate Sodium, USP	Docusate Sodium	
(b) (4)		
Talc, USP	Talc	
Calcium Stearate, NF		
	Magnesium Stearate	

Inactive ingredients[12]

(b) (4)	Amount (mg)/Tablet	Maximum Daily amount (mg)	IIG Limit (mg)
(b) (4)			(b) (4)
Lactose (b) (4) NF (b) (4)			
Povidone, USP (b) (4)			
Docusate Sodium, USP			
Talc, USP			
Calcium Stearate, NF			

Note for IIG:
The maximum daily dose of nilutamide tablets is 300 mg (2 x 150 mg). The IIG limits of all inactive ingredients are acceptable.

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Acceptable

[12] FDA inactive ingredient guide: http://intranetapps.test.fda.gov/scripts/iig/

4.3 Dissolution Data

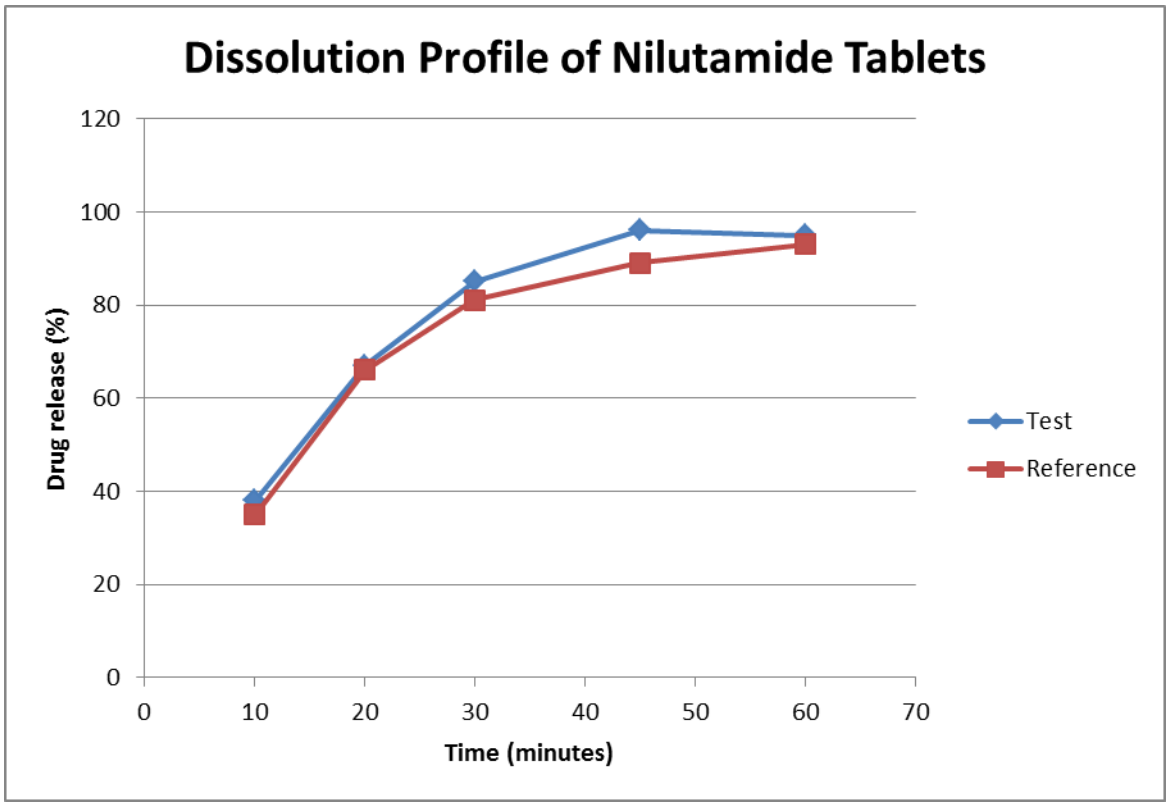
Dissolution Review Path	DARRTS, ANDA 207631, REV-BIOEQ-02 (Dissolution Review) Final Date: 09/12/2014 and 9/25/2014

Table 20. Dissolution Data

Dissolution Conditions	**Apparatus:**	Apparatus II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	5.4 g/L Sodium Lauryl Sulfate
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	Not Less Than (NLT) (b) (4)	
Dissolution Testing Site (Name, Address)	ANI Pharmaceuticals, Inc. 210 Main Street West, Baudette, MN 56623	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Dt.) (Reference – Exp. Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
Study Report #: N/A	05/14/13	Nilutamide Tablets Batch No.: C-0404-31 Mfg Date: April 9, 2013	150 mg Tablet	12	Mean (%)	38	67	85	96	95	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	9	6	4	2	3	
Study Report #: N/A	05/13/14	Nilandron® (Nilutamide Tablets) Batch No.:2AL3A Exp. Date:	150 mg Tablet	12	Mean (%)	35	66	81	89	93	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	8	8	6	4	3	

Figure 2. Dissolution Profiles



Note for dissolution testing:

The firm developed its own dissolution method for nilutamide tablets. The firm's dissolution method was acceptable and the firm accepted the FDA-recommended dissolution specifications of NLT (b) (4)

4.4 SAS Output

4.4.1 Steady Sate Study Data

sub (b) (6)	seq	per	trt	group	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	K
	2	1	2	1	2938.62	3203.67	4253.59	4112.22	3685.54	4024.93	4122.14	3784.78	3990.23	4032.23	3575.26	3215.88	3129.47	2865.10	
	2	2	1	1	2678.53	3413.11	3801.89	3853.32	3723.75	4308.05	4536.26	3535.22	3425.23	3206.34	2752.18	2685.78	3353.71	2804.41	
	1	1	1	1	3863.83	4000.04	4363.02	4251.35	4547.58	5504.44	5719.07	5359.56	5640.42	4580.16	4161.41	4053.33	4067.29	3817.64	
	1	2	2	1	2907.75	4241.20	4256.19	4313.23	4568.34	5494.40	5161.26	4845.79	4768.42	4628.49	3586.96	3807.04	3669.68	3395.62	
	2	1	2	1	3414.97	3606.24	4260.68	3987.29	4584.13	4649.06	4749.47	4697.84	4541.50	4055.03	3504.26	3383.30	3677.03	4568.04	
	2	2	1	1	3839.24	4044.29	5161.07	4744.26	4305.89	4762.12	5029.29	4834.92	5245.31	4685.88	3756.42	4278.72	4148.66	3609.08	
	1	1	1	1	3073.54	3142.20	3712.61	4253.56	4212.06	3981.48	4200.59	4168.80	4204.60	3552.55	3344.25	3200.00	4370.78	2736.75	
	1	2	2	1	3378.03	3841.15	4353.03	4230.83	4174.73	4375.11	4511.74	4560.67	4344.87	4558.20	3292.97	2969.19	3418.27	3140.41	
	2	1	2	1	2925.58	3528.74	4400.30	4271.68	4337.09	4315.46	4201.66	4530.59	4543.16	4201.41	3897.83	3659.27	3592.39	2879.38	
	2	2	1	1	3416.23	4391.28	5209.37	5066.65	3953.59	4424.20	4433.97	4373.71	4417.41	4049.74	3100.57	2967.27	3204.37	3179.61	
	2	1	2	1	2830.39	3063.76	3660.33	3899.19	3786.05	3853.86	3656.78	3790.47	3930.20	3635.08	3429.74	3081.05	2906.80	2639.56	
	2	2	1	1	2512.41	2822.87	4130.36	3974.41	4006.30	2951.98	3786.34	3965.20	4087.85	3518.56	3235.02	2870.63	2805.84	2393.48	
	2	1	2	1	3331.63	4705.10	4143.75	4199.58	4345.72	4067.78	4299.25	4098.23	4108.84	3717.92	3056.42	3250.75	3086.92	3043.64	
	2	2	1	1	3219.17	4047.64	4513.05	4137.30	4409.91	4433.53	4322.81	4505.23	4513.20	4608.10	4092.95	2547.09	4028.87	3371.33	
	1	1	1	1	2402.55	2464.99	3256.77	3545.78	3477.46	3328.35	3255.41	3204.21	3326.42	3252.10	2792.52	2695.84	2501.15	2399.25	
	1	2	2	1	1678.92	2164.14	3177.30	2791.56	2699.31	2650.19	2586.68	2560.06	2613.58	2499.77	2032.46	1932.70	2141.03	1919.04	
	1	1	1	1	2674.91	2945.53	3065.06	3685.65	3964.85	3728.08	3951.29	3761.45	4019.32	3370.63	3175.17	3051.12	2757.21	2867.95	
	1	2	2	1	2750.98	3016.66	3836.29	4079.32	3905.31	4000.80	4163.10	3990.59	4151.52	3591.66	3130.17	2764.30	3135.15	2610.88	
	2	1	2	1	1527.09	2500.89	2727.77	2566.29	2651.06	2399.06	2616.23	2424.69	2460.29	2266.89	2014.44	1963.69	1681.78	1600.93	
	2	2	1	1	1774.93	1804.47	1863.12	1929.88	2641.63	2865.08	2839.90	2832.62	2901.22	2157.06	2013.69	1830.68	1950.44	1754.48	
	2	1	2	1	2248.49	2406.42	2659.30	3618.13	3138.44	3440.27	3340.09	3359.18	3294.72	3226.33	2792.25	2993.24	2796.81	2590.09	
	2	2	1	1	2825.31	2988.01	4167.90	3737.10	3434.97	3587.47	3633.15	3530.22	3761.64	3407.78	3188.42	2996.47	3701.87	2805.21	
	2	1	2	2	2337.65	3093.22	3873.00	3967.40	3689.90	3938.16	4068.04	3666.93	3486.39	3612.51	2970.93	3069.44	2879.06	2318.12	
	2	2	1	2	2105.25	2820.61	4271.06	4412.81	4401.47	3497.49	3392.57	3398.94	3513.01	3286.82	2685.32	2794.59	2656.01	1856.42	
	2	1	2	2	2591.84	2658.52	2576.93	3543.98	3880.93	4016.79	3909.82	3623.99	3082.24	3312.31	2804.77	2920.54	2387.56	2476.51	
	2	2	1	2	3537.34	3636.76	3944.49	4156.29	4488.59	4824.56	4204.20	3874.53	4068.48	4500.36	3181.60	3125.84	2744.87	2979.14	
	1	1	1	2	3201.96	3987.41	4245.62	4318.03	4905.80	4786.14	4373.58	4534.84	3979.02	4207.21	3131.19	3365.82	3079.34	2935.93	
	1	2	2	2	3037.71	4149.76	4528.56	4467.09	4300.45	4611.49	4260.46	4193.17	4041.70	3807.97	3760.92	3113.66	2853.88	2750.37	
	2	1	2	2	2213.34	2908.07	3290.40	3169.08	2875.75	3045.10	3432.95	2927.17	3049.08	2800.53	2393.90	2489.71	1951.87	2288.87	
	2	2	1	2	2253.70	3203.15	3040.20	3089.69	2776.94	3000.76	3075.94	2999.59	2974.89	2316.96	2805.14	2206.02	2052.33	2133.01	
	1	1	1	2	3105.00	3352.96	4478.06	4188.85	4065.00	4510.08	4457.60	4101.48	4198.77	4013.57	3472.49	3665.26	3535.88	2885.02	
	1	2	2	2	3593.62	3675.43	4224.81	4551.03	4590.85	4504.72	4613.56	4603.14	4193.71	4280.19	4083.47	4186.85	3829.47	3514.26	
	2	1	2	2	2229.92	2382.92	2762.39	2855.44	3807.70	3635.41	3899.29	3831.34	3692.75	3759.03	3186.38	3061.87	2982.58	2483.85	
	2	2	1	2	2560.39	3578.50	3832.05	3542.02	3105.44	3031.94	3392.17	3365.41	3622.56	3321.12	2995.96	3185.26	2958.74	2428.65	
	1	1	1	2	2976.50	3969.45	4293.83	3920.97	4126.81	4176.64	4335.32	4854.08	3981.38	3861.19	3604.31	3175.79	3032.48	3179.44	

sub (b) (6)	seq	per	trt	group	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	k
	1	2	2	2	2762.94	3366.88	4222.70	4514.42	4354.76	4283.32	3992.62	4428.60	4028.57	3880.91	3587.57	3347.38	3535.74	3038.39	
	1	1	1	3	3396.59	3572.21	3650.95	3595.05	4523.66	4533.07	4312.93	4230.23	4273.33	3111.32	3081.86	3140.84	3208.71	3242.31	
	1	2	2	3	3428.03	4383.71	2504.70	4513.70	4459.61	4442.35	4718.27	4470.30	4274.74	3706.50	2379.28	3174.48	3248.09	3554.77	
	1	1	1	3	2164.26	3349.83	2873.59	2951.81	3104.29	3102.14	2921.34	2817.09	2776.24	2365.36	2046.56	2119.34	1824.67	1671.51	
	1	2	2	3	2129.90	2142.63	4804.84	3296.47	3291.51	3667.82	3069.52	3417.19	3353.86	3048.24	3391.53	2252.50	2048.42	2031.15	
	2	1	2	3	2465.52	2319.77	2652.75	3489.55	4106.47	4005.17	3860.20	4126.69	3908.39	2675.38	2562.47	2841.16	2673.58	2538.70	
	2	2	1	3	2520.16	3101.01	3505.09	4015.46	3964.48	4076.62	4832.61	3648.24	3399.92	3335.41	2640.56	2496.91	2285.73	2176.20	
	1	1	1	3	1999.58	2098.73	2076.19	2172.74	2109.78	2039.67	2103.26	2001.05	2150.86	2144.59	1953.59	1938.14	1773.25	1870.40	
	1	2	2	3	2582.76	2949.61	3166.73	3167.38	3530.92	4232.67	4102.29	3751.31	3721.70	3559.72	3088.72	2752.92	2656.82	2612.96	
	1	1	1	3	3142.51	3047.30	3582.97	4435.03	4327.57	4316.15	4250.55	4150.85	3996.47	3643.70	3466.86	3017.98	2684.85	3159.07	
	1	2	2	3	2992.15	3487.95	3353.44	4252.54	2844.16	3873.30	2962.10	3585.36	3972.27	3465.67	3381.40	2355.84	3071.77	3089.36	
	1	1	1	3	1203.06	1153.07	2035.75	2369.23	2326.56	2115.80	2065.12	2091.34	1893.05	1670.50	1461.62	1470.39	1264.77	1488.93	
	1	2	2	3	1627.65	1508.44	1620.32	2588.46	2614.36	2472.71	2555.33	2385.10	2338.59	2518.72	2254.86	1821.50	1742.02	1892.42	
	1	1	1	3	4241.86	4105.77	4792.36	5291.60	5230.92	4815.81	4528.08	4484.74	4093.68	3771.18	3715.24	3698.68	3849.78	3623.14	
	1	2	2	3	3686.97	3696.92	3757.09	3835.18	3735.14	3771.61	4902.15	3958.36	3829.46	4061.62	4313.21	3647.88	3620.99	2912.53	
	1	1	1	3	1944.71	1816.16	2038.21	2280.42	2730.07	3061.70	2943.32	3048.35	3025.28	2683.24	2565.01	2510.47	2659.22	1886.37	
	1	2	2	3	2155.11	1997.66	1857.97	2391.31	2983.09	3069.52	3275.00	3071.40	2865.35	3132.73	3201.37	2509.88	2574.96	1976.48	
	2	1	2	3	2501.14	2189.67	2508.88	3526.44	3588.31	3316.09	3401.63	2941.00	2814.91	2664.02	2679.27	3025.70	2830.03	2494.23	
	2	2	1	3	2958.11	3259.00	3635.37	3587.62	3454.69	3171.63	3356.83	3245.01	3186.63	3762.33	3670.73	3127.37	3217.48	2871.40	
	1	1	1	3	2985.30	3148.25	3229.73	4626.14	4300.06	4408.44	4154.88	4149.34	4152.78	3760.17	3248.87	3150.63	2938.62	2769.79	
	1	2	2	3	3083.90	3395.46	3747.39	4559.20	4496.15	4525.92	3709.16	4020.64	4111.98	3938.79	3719.12	3399.86	2995.47	3023.51	
	1	1	1	3	3219.63	3300.10	4612.61	4623.86	4677.75	4726.32	4563.19	4463.24	4281.97	4205.28	3564.44	3297.55	2996.41	3092.59	
	1	2	2	3	3377.46	3320.64	3844.99	4296.96	4620.04	3982.46	4658.20	4492.36	4109.46	4146.75	3869.93	3403.85	3372.41	3298.39	
	2	1	2	3	2903.39	2849.12	3569.31	3584.58	3588.31	3896.00	3937.93	4021.65	3848.13	4058.97	3467.79	2997.42	3142.74	2934.75	
	2	2	1	3	2943.40	3130.62	3221.78	3655.43	3437.78	3791.10	4052.73	4347.60	4248.22	3878.96	3698.24	3364.54	3293.05	2753.94	
	2	1	2	3	2693.17	2975.60	3415.68	3731.39	3764.27	3937.25	3959.24	3526.06	3438.79	3424.23	2955.83	2716.50	2841.27	2513.68	
	2	2	1	3	2922.16	3610.48	4124.58	4205.84	3731.78	4087.34	4005.87	3726.77	3932.65	4120.25	3516.45	2666.52	3288.20	2630.70	
	1	1	1	3	2716.02	3418.70	3684.87	3872.24	3295.75	3662.39	3667.20	3450.63	3646.44	3461.59	2754.01	2341.20	2419.61	2173.96	
	1	2	2	3	3075.56	3200.37	4008.57	4161.90	4044.38	3800.29	3971.05	3774.90	3572.54	2608.21	3124.20	2569.40	2509.59	2990.70	
	2	1	2	3	2937.99	3122.43	4297.38	4710.68	4527.90	3933.92	4097.78	3939.54	3757.52	4111.36	3911.09	3497.65	3461.75	2948.58	
	2	2	1	3	3316.39	3281.10	3519.56	3651.62	3685.27	4969.09	3763.18	3966.66	2553.28	4370.08	3978.90	3584.61	2993.10	3385.12	
	2	1	2	3	3236.98	3407.31	3653.10	3829.09	3758.96	3882.28	3734.65	3803.69	3644.60	3937.58	3376.26	3732.07	3401.58	2990.04	
	2	2	1	3	2937.28	3746.12	3690.56	3770.61	3891.03	3649.97	3164.83	2972.02	3060.55	3423.62	3692.44	3305.32	3226.85	2905.24	
	1	1	1	3	3308.08	3267.12	3467.09	3926.87	4254.17	4590.56	5355.97	5507.82	4971.58	4477.55	3881.35	3371.01	3239.62	3780.74	
	1	2	2	3	2935.54	2925.93	3075.39	3554.56	4346.34	4732.96	4841.66	4948.86	5626.55	4573.27	4079.69	3376.12	3240.42	3035.72	
	1	1	1	3	2522.85	3058.83	3886.92	3867.50	3738.63	3818.37	3896.17	3669.43	3803.23	3629.85	3313.08	3152.93	2930.76	2365.36	
	1	2	2	3	2939.25	2937.06	3906.72	4517.22	4543.12	4488.43	5693.44	4472.65	4240.25	3893.70	3659.16	3245.62	3100.21	2738.43	

Obs	sub (b) (6)	seq	per	trt	group	AUCT	AUCI	CMAX	CAVG	TMAX	SWING	FLUCT
1		2	1	2	1	78589.84	2865.10	4253.59	3274.58	1.0	0.48462	42.402

Obs	sub (b) (6)	seq	per	trt	group	AUCT	AUCI	CMAX	CAVG	TMAX	SWING	FLUCT
2		2	2	1	1	75872.40	2678.53	4536.26	3161.35	3.0	0.69356	58.764
3		1	1	1	1	100495.23	3817.64	5719.07	4187.30	3.0	0.49807	45.410
4		1	2	2	1	91904.66	2907.75	5494.40	3829.36	2.5	0.88957	67.548
5		2	1	2	1	95812.98	3383.30	4749.47	3992.21	3.0	0.40380	34.221
6		2	2	1	1	99335.12	3609.08	5245.31	4138.96	4.0	0.45336	39.532
7		1	1	1	1	87313.15	2736.75	4370.78	3638.05	12.0	0.59707	44.915
8		1	2	2	1	83720.65	2969.19	4560.67	3488.36	3.5	0.53600	45.623
9		2	1	2	1	85972.91	2879.38	4543.16	3582.21	4.0	0.57782	46.446
10		2	2	1	1	82408.49	2967.27	5209.37	3433.69	1.0	0.75561	65.297
11		2	1	2	1	73625.09	2639.56	3930.20	3067.71	4.0	0.48896	42.072
12		2	2	1	1	70303.31	2393.48	4130.36	2929.31	1.0	0.72567	59.293
13		2	1	2	1	79856.20	3043.64	4705.10	3327.34	0.5	0.54588	49.934
14		2	2	1	1	90222.14	2547.09	4608.10	3759.26	5.0	0.80916	54.825
15		1	1	1	1	64295.02	2399.25	3545.78	2678.96	1.5	0.47787	42.797
16		1	2	2	1	51683.57	1678.92	3177.30	2153.48	1.0	0.89247	69.580
17		1	1	1	1	72786.30	2674.91	4019.32	3032.76	4.0	0.50260	44.329
18		1	2	2	1	74623.74	2610.88	4163.10	3109.32	3.0	0.59452	49.922
19		2	1	2	1	45409.36	1527.09	2727.77	1892.06	1.0	0.78626	63.459
20		2	2	1	1	47808.04	1754.48	2901.22	1992.00	4.0	0.65360	57.567
21		2	1	2	1	68323.54	2248.49	3618.13	2846.81	1.5	0.60913	48.111
22		2	2	1	1	79693.01	2805.21	4167.90	3320.54	1.0	0.48577	41.038
23		2	1	2	2	70565.90	2318.12	4068.04	2940.25	3.0	0.75489	59.516
24		2	2	1	2	64343.65	1856.42	4412.81	2680.99	1.5	1.37706	95.353
25		2	1	2	2	65305.76	2387.56	4016.79	2721.07	2.5	0.68238	59.875
26		2	2	1	2	76984.48	2744.87	4824.56	3207.69	2.5	0.75767	64.835
27		1	1	1	2	80612.25	2935.93	4905.80	3358.84	2.0	0.67095	58.647
28		1	2	2	2	77169.75	2750.37	4611.49	3215.41	2.5	0.67668	57.882
29		2	1	2	2	56873.10	1951.87	3432.95	2369.71	3.0	0.75880	62.501
30		2	2	1	2	55747.15	2052.33	3203.15	2322.80	0.5	0.56074	49.545
31		1	1	1	2	84317.59	2885.02	4510.08	3513.23	2.5	0.56328	46.256
32		1	2	2	2	94112.72	3514.26	4613.56	3921.36	3.0	0.31281	28.034
33		2	1	2	2	71402.22	2229.92	3899.29	2975.09	3.0	0.74862	56.111
34		2	2	1	2	70893.41	2428.65	3832.05	2953.89	1.0	0.57785	47.510
35		1	1	1	2	80700.16	2976.50	4854.08	3362.51	3.5	0.63080	55.839
36		1	2	2	2	84114.44	2762.94	4514.42	3504.77	1.5	0.63392	49.974
37		1	1	1	3	80543.32	3081.86	4533.07	3355.97	2.5	0.47089	43.242
38		1	2	2	3	82921.58	2379.28	4718.27	3455.07	3.0	0.98307	67.697
39		1	1	1	3	49602.89	1671.51	3349.83	2066.79	0.5	1.00408	81.204
40		1	2	2	3	58450.97	2031.15	4804.84	2435.46	1.0	1.36558	113.888
41		2	1	2	3	67491.37	2319.77	4126.69	2812.14	3.5	0.77893	64.254

Obs	sub	seq	per	trt	group	AUCT	AUCI	CMAX	CAVG	TMAX	SWING	FLUCT
42	(b) (6)	2	2	1	3	62881.70	2176.20	4832.61	2620.07	3.0	1.22067	101.387
43		1	1	1	3	45711.55	1773.25	2172.74	1904.65	1.5	0.22529	20.974
44		1	2	2	3	69271.33	2582.76	4232.67	2886.31	2.5	0.63882	57.163
45		1	1	1	3	76169.33	2684.85	4435.03	3173.72	1.5	0.65187	55.146
46		1	2	2	3	74622.19	2355.84	4252.54	3109.26	1.5	0.80511	61.002
47		1	1	1	3	36124.83	1153.07	2369.23	1505.20	1.5	1.05472	80.797
48		1	2	2	3	46689.41	1508.44	2614.36	1945.39	2.0	0.73315	56.848
49		1	1	1	3	93732.53	3623.14	5291.60	3905.52	1.5	0.46050	42.721
50		1	2	2	3	85540.20	2912.53	4902.15	3564.18	3.0	0.68312	55.823
51		1	1	1	3	58368.40	1816.16	3061.70	2432.02	2.5	0.68581	51.214
52		1	2	2	3	59933.77	1857.97	3275.00	2497.24	3.0	0.76267	56.744
53		2	1	2	3	66838.15	2189.67	3588.31	2784.92	2.0	0.63875	50.222
54		2	2	1	3	76603.38	2871.40	3762.33	3191.81	5.0	0.31028	27.913
55		1	1	1	3	76082.37	2769.79	4626.14	3170.10	1.5	0.67021	58.558
56		1	2	2	3	79903.74	2995.47	4559.20	3329.32	1.5	0.52203	46.968
57		1	1	1	3	81471.37	2996.41	4726.32	3394.64	2.5	0.57733	50.960
58		1	2	2	3	85467.05	3298.39	4658.20	3561.13	3.0	0.41227	38.185
59		2	1	2	3	77338.69	2849.12	4058.97	3222.45	5.0	0.42464	37.544
60		2	2	1	3	79128.54	2753.94	4347.60	3297.02	3.5	0.57868	48.336
61		2	1	2	3	69726.86	2513.68	3959.24	2905.29	3.0	0.57507	49.756
62		2	2	1	3	76910.63	2630.70	4205.84	3204.61	1.5	0.59875	49.152
63		1	1	1	3	62956.56	2173.96	3872.24	2623.19	1.5	0.78119	64.741
64		1	2	2	3	69952.60	2509.59	4161.90	2914.69	1.5	0.65840	56.689
65		2	1	2	3	83723.85	2937.99	4710.68	3488.49	1.5	0.60337	50.815
66		2	2	1	3	81510.06	2553.28	4969.09	3396.25	2.5	0.94616	71.132
67		2	1	2	3	81928.36	2990.04	3937.58	3413.68	5.0	0.31690	27.757
68		2	2	1	3	77596.77	2905.24	3891.03	3233.20	2.0	0.33931	30.489
69		1	1	1	3	88754.50	3239.62	5507.82	3698.10	3.5	0.70014	61.334
70		1	2	2	3	84125.54	2925.93	5626.55	3505.23	4.0	0.92300	77.045
71		1	1	1	3	72147.47	2365.36	3896.17	3006.15	3.0	0.64718	50.923
72		1	2	2	3	79545.91	2738.43	5693.44	3314.41	3.0	1.07909	89.156

4.4.2 Steady Sate Study Codes

```
/*=================================================================
===========
/ Program    : TWOWAYCONTINU(2)07MAR2009.SAS (Updated: 27 March 2007)
/ SubMacros  : macrolib.sas, continu2.sas, continu.sas,
/ Purpose    : To analyze two-way crossover bioequivalence studies.
/ Notes      :
/
```

```
/=====================================================================
==========
/ PARAMETERS:
/-------name------- ------------------------description--------------
----------

/=====================================================================
==========
/ AMENDMENT HISTORY:
/ Init --Date--  ---------------------Description--------------------
----
/ ELIMINATE CALCKE OPTION FROM THIS SAS PROGRAM,
  FOR CALCKE OPTION, PLEASE USE TWOWAYCALCKE07MAR2009.SAS
/=====================================================================
==========*/
**** NODATE OPTION generates error in word document.. with bodytitle
ods ****;

**********FOLLOW THE STEPS 1-15 TO RUN THIS PROGRAM**********;

OPTIONS PS=60;

****** STEP 1:  LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION
IF APPLICABLE ********;
%INCLUDE "y:\division\bio\sas programs\macros\MACROLIB.SAS";

/*********************************************************
  ASSIGN WHETHER HAVE GROUP EFFECT:
   TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
   TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
   TRTGROUP =        NO GROUP EFFECT IN STUDY
 NOTE:  group variable has to be named GRP in the dataset.
*********************************************************/;

*****STEP 2:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = Nilutamide;
%let drug=Nilutamide Tablets;
%let dose= 1 x 150 mg;
%let anda=207631;
%let studytype=Fasting;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Users\PARKE\Documents\ADBII\A-Reviews\Nilutamide\Stat;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;


**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level..doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
```

```
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level..doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level..png;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;


%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;


*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM******;

/***SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
***/
/***SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S
KE WILL BE
USED FOR CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR
SUPPLIED
PARAMETERS.  FOR STATISTICS ON CALCULATED PARAMETERS USE CONTINU2.SAS
***/

%LET FNAME=%QUOTE(y:\division\bio\sas programs\macros\CONTINU.SAS);
*%LET FNAME=%QUOTE(DESKTOP\CONTINU2.SAS);
/*** WRITE DATA FILE NAMES  ***/

*****STEP 7: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND
VARIABLE LIST *****;

/*** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE
THE NEXT LINE */
FILENAME ORGPLASM DDE 'EXCEL|conc2!R2C1:R73C19';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */
 *%LET VARPLASM=SUB SEQ PER TRT c1-c22;  /* VARIABLE LIST FOR THE
PLASMA DATA FILE */
%LET PLASMLS=900;   /* INCREASE LINE SIZE IF NEEDED */
 *%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 *RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R73C26';


** IF INPUT FILE IS A SAS DATASET **;
** SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED **;
LIBNAME libdata "&studydir";

** STEP 8:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
```

```
DATA PLASMA;

*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST
SPECIFYING DATA POINTS TO BE USED FOR CALCULATION OF KE **;
  infile orgplasm;
  input sub seq per trt group c1-c14;

  KE_FIRST = 9;
  KE_LAST=14;

RUN;

proc print data=plasma;
run;


%SORTDS(PLASMA, &VARSORT)
RUN;



*****STEP 9:PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND
VARIABLE LIST *****;

/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4
***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE
THE NEXT LINE */
FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R73C12';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT AUCT AUCI CMAX TMAX KE THALF; /*
VARIABLE LIST */
%LET PARAMLS=500;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
  infile orgparam;
  input sub seq per trt group AUCT AUCI CMAX CAVG TMAX SWING FLUCT


/* AUCI is CMIN */

 RUN;


%SORTDS(PARAME, &VARSORT)
RUN;
```

```
*****STEP 10: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY
*****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12,
C13, C14);


/***STEP : USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                   ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE
THE TIME,
                   OR ADD FEW DEVIATED SAMPLING TIME POINTS,
                   ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/

%LET TIME=%STR(T1=0; T2=0.5; T3=1.0; T4=1.5; T5=2; T6=2.5;
T7=3; T8=3.5; T9=4; T10=5; T11=6; T12=8; T13=12; T14=24.0);


*IF SUB=1 AND PER=2 THEN T12=5;
*IF SUB=12 AND PER=2 THEN T7=1.8);*/

/***STEP 11A:  USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME
DATASET INCLUDED
                   IN THE CONCENTRATION DATASET,
                  ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;
/*
DATA TIME;
SET PLASMA;
*FILE'DESKTOP\TIME';
PUT SUB TRT SEQ PER GRP;
KEEP SUB TRT SEQ PER GRP;

PROC PRINT DATA=TIME;RUN;
*/
*****STEP 12: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=14;


*****STEP 13 : INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF
THESE ARE NOT
IN THE DATA SUBMITTED. *****;
*%LET KE FIRST=&NO ASSAY-2;
*%LET KE_LAST=&NO_ASSAY;


*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/***VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL***/
/***LEAVE AS IT IS IF NO CHANGE IS DESIRED***/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
```

```
*****STEP 15: IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR
MODIFIED *****;
/***CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC  ***/

CLOSED ***/
/* %LET ADD VAR=%STR(KE FIRST=&KE FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );  */



DATA ORIGIN;
       ARRAY C(&NO ASSAY) C1-C&NO ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
SET PARAME;
* SET TIME;
*SET MERGED;
&TIME;
*KE_FIRST=0;
*KE LAST=0;
CLAST=C&NO ASSAY;
NEWCMAX=MAX(&CONCENT);


/***DO NOT CHANGE: TITLES FOR TABLES***/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/*** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ***/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST   2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;


%COPYDS(ORIGIN, NEW)
RUN;


*****STEP 14: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)



***************DO NOT CHANGE ANY OF THE STATMENTS BELOW THIS LINE
***************;
***************YOU CAN NOW SUBMIT/RUN THE
PROGRAM*********************************;
```

```
%*ADDVARIA(NEW, NEW)
RUN;

%RITEDATA(NEW, NEW, SUB TRT KE_FIRST KE_LAST) /****** TO EDIT KE-FIRST
AND KE-LAST**/
RUN;

%COPYDS(NEW, NEWCONC)
RUN;

** CHECK >0 CONC FOR C1 **;
title "PRE-DOSE CONC GREATER THAN 0";

data predose;
  set origin(where=(c1 > 0));


  maxlimit = 0.05*cmax;

  if c1 > maxlimit then flag = 1;
  else flag=0;
run;

proc print data=predose;
run;

*** dataset for data _null_***;
data updatedconc;
  set new;
run;


DATA NEWCONC;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
I=I;
OUTPUT;
END;


proc template;
  define style mystyle;
  parent = styles.rtf;
    REPLACE fonts /
       'headingFont' = ("Arial", 8pt,Bold)
       'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
       'TitleFont' = ("Arial",8pt,Bold)
       'StrongFont' = ("Arial",8pt,Bold)
```

```
        'EmphasisFont' = ("Arial",8pt)
        'FixedEmphasisFont' = ("Arial",8pt)
        'FixedStrongFont' = ("Arial",8pt,Bold)
        'FixedHeadingFont' = ("Arial",8pt,Bold)
        'BatchFixedFont' = ("Arial",8pt)
        'FixedFont' = ("Arial",8pt)
        'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /
      outputwidth = 85%
      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 0.25in
        leftmargin = 0.25in;
  END;
run;

proc template;
  define style mystyle1;
  parent = styles.rtf;
    REPLACE fonts /
       'headingFont' = ("Arial", 8pt,Bold)
       'docFont' = ("Arial", 8pt)
     'TitleFont2' = ("Arial",8pt,Bold)
       'TitleFont' = ("Arial",8pt,Bold)
       'StrongFont' = ("Arial",8pt,Bold)
       'EmphasisFont' = ("Arial",8pt)
       'FixedEmphasisFont' = ("Arial",8pt)
       'FixedStrongFont' = ("Arial",8pt,Bold)
       'FixedHeadingFont' = ("Arial",8pt,Bold)

       'FixedFont' = ("Arial",8pt)
       'headingEmphasisFont' = ("Arial",8pt,Bold);

    style SysTitleAndFooterContainer from Container /
      outputwidth = 85%
      cellpadding = 2
      cellspacing = 2
      borderwidth = 0;

      REPLACE Body from Document /
        bottommargin = 1.0in
        topmargin = 1.0in
        rightmargin = 1in
        leftmargin = 1in;
  END;
run;



options orientation=landscape papersize=letter;
```

```
ods rtf file="&concoutput" style=mystyle bodytitle;

TITLE "&STUDYTYPE CONCENTRATION DATASET";
proc print data=plasma;
run;

TITLE "&STUDYTYPE PHARMACOKINETIC DATASET";
proc print data=parame;
run;
ods rtf close;



/* DETERMINE NEWTMAX, KE_FIRST, KE_LAST, NEWAUCT AND AUCLST */
DATA NEW;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO ASSAY) T1-T&NO_ASSAY;
       NO_ASSAY=&NO_ASSAY;
SET NEW;
CLAST=C&NO ASSAY;
NEWCMAX=MAX(&CONCENT);



/* CALCULATE THALF IF THALF IS NOT GIVEN */
/* THALF=LOG(2)/KE;  */

DO I=1 TO NO_ASSAY;
IF C(I)=NEWCMAX THEN NEWTMAX=T(I);
END;
/* INTERPOLATE MISSING VALUE ON LINEAR SCALE */
IF C(1)=. THEN C(1)=0;  /* MISSING VALUE */


   H=I-1;
   J=I+1;
IF C(I)=. THEN DO;    /* FIRST MISSING VALUE */


C(I)=C(H)+((C(J)-C(H))/(T(J)-T(H)))*(T(I)-T(H));
    END;
    END;
NEWTMAX=NEWTMAX;
/* CALCULATE AUCLST(TO THE LAST SAMPLING TIME POINT) */
AUCLST=0;
DO I=2 TO NO_ASSAY;
K=I-1;
AUCLST=AUCLST+((C(K)+C(I))*(T(I)-T(K))/2);
END;

/* CALCULATE AUCT AND STORE AS NEWAUCT(TO THE LAST DETECTABLE
CONC) */
DO I=NO ASSAY TO 2 BY -1;
IF C(NO_ASSAY)>0 THEN DO;

       CLAST=C(NO_ASSAY);
```

```
       GOTO F;
       END;
   ELSE DO;
        K=I-1;
        IF C(I)=0 AND C(K)>0 THEN DO;
           NEWAUCT=AUCLST-(C(I)+C(K))*(T(I)-T(K))/2;
           CLAST=C(K);
           GOTO F;
           END;
    END;
END;

F: NEWAUCT=NEWAUCT; /* FLAG TO CONTINUE */
NEWAUCI=NEWAUCT+CLAST/KE;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
IF CONC=0 OR CONC=. THEN LOGCONC=.;
ELSE LOGCONC=LOG(CONC);
NEWAUCT=NEWAUCT;
I=I;
OUTPUT;
END;
/* PROC PRINT;



data  null ;
  set updatedconc(where=(trt=1)) end=last;

  if last then call symput('testsub',trim(left(_N_)));
run;


data _null_;
  set updatedconc(where=(trt=2)) end=last;

  if last then call symput('refsub',trim(left(_N_)));
run;

/* PROC GLM  CALCULATE LSMEANS */
%MACRO GRPANALYSIS(TRTGP=);

      /** TRTGRP INTERACTION **/
      %if &trtgp=1 %then
      %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ
GRP,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,per GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT
TRT*GRP,SEQ GRP,SUB(SEQ*GRP))
      RUN;
      %end;

      /** No TRT*GRP Interaction **/
      %else %if &trtgp=2 %then
```

```
      %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ
GRP,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,per GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT,SEQ
GRP,SUB(SEQ*GRP))
      RUN;
      %end;

      /** NO GROUP EFFECT **/
      %else %do;
      %PROCGLM(BASE,2,SUB TRT PER SEQ,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
      , , , , , ,SEQ SUB(SEQ) PER TRT,SEQ,SUB(SEQ))
      RUN;
      %end;

%MEND GRPANALYSIS;

/* STATISTICS ON SUBMITTED DATA WITHOUT RECALCULATION */
DATA BASE;
SET NEW;
IF I=NO_ASSAY;

LAUCT=LOG(AUCT);
LAUCI=LOG(AUCI);
LCMAX=LOG(CMAX);
AUCRATIO=AUCT/AUCI;
OUTPUT;


/* TO RECALCULATE KE  */
%INCLUDE "&FNAME";

/* PRINT SUMMARY OF PARAMETERS */
%LET TITLE=SUMMARY OF PARAMETERS;
%*PRINT(BASE, &TITLE)



options orientation=portrait papersize=letter;

TITLE "&STUDYTYPE STATISTICAL OUTPUT";
ods rtf file="&odsfile" style=mystyle1 bodytitle;

ods graphics off;

ods rtf exclude LSMeans;
ods rtf exclude AUCT.OverallANOVA
                AUCT.FitStatistics
                        AUCT.ModelANOVA
                        AUCT.AltErrTests
                        AUCT.Estimates
                        AUCI.OverallANOVA
                AUCI.FitStatistics
                        AUCI.ModelANOVA
                        AUCI.AltErrTests
                        AUCI.Estimates
                        CMAX.OverallANOVA
```

```
                CMAX.FitStatistics
                        CMAX.ModelANOVA
                        CMAX.AltErrTests
                        CMAX.Estimates
                      AUCT.MeanPlot
                        AUCT.DiffPlot
                        AUCI.MeanPlot
                      AUCI.DiffPlot
                        CMAX.MeanPlot
                        CMAX.DiffPlot

                        LAUCT.MeanPlot
                        LAUCT.DiffPlot
                        LAUCI.MeanPlot
                      LAUCI.DiffPlot
                        LCMAX.MeanPlot
                        LCMAX.DiffPlot;



ods listing exclude LSMeans;

ods output "Estimates"=estimates;

%GRPANALYSIS(TRTGP=&TRTGROUP);


ods graphics on;

DATA GLMOUT;
SET GLMOUT;
RENAME _NAME_=NNAME;
DATA LSMOUT;
SET LSMOUT;
RENAME _NAME_=NNAME;
/* TRANSFER DF FROM GLMOUT TO LSMOUT3 FOR CI CALCULATIONS */
DATA GLMOUT1;
SET GLMOUT;
IF _SOURCE_='ERROR';
IF NNAME='AUCT' OR
 NNAME='AUCI' OR
 NNAME='CMAX';
/* KEEP NNAME  SOURCE  DF; */
%SORTDS(GLMOUT1, NNAME)
RUN;
%*PRINT(GLMOUT1,GLMOUT1)
RUN;
%*LET TITLE=LSMEANS AND STANDARD ERRORS;
%*PRINT(LSMOUT, &TITLE)
RUN;

/* CALCULATE T AND 90% CI FOR NON-TRANSFORMED DATA */
%LSMFILE(LSMOUT,TRT,2,AUCT,AUCI,CMAX,X,X,X,NNAME, OR)
RUN;
```

```
%MERGMULT(2,LSMOUT,GLMOUT1, , ,LSMDAT,NNAME)
RUN;
DATA LSMDAT;
SET LSMDAT;
/* FOR 90% CI, P=0.95 */

/* CACULATION OF T BASED ON P AND DF */
%CI(0.95,2);

RUN;

%LET TITLE=90% CONFIDENCE INTERVALS ON NON-TRANSFORMED DATA;
%*PRINT(LSMDAT, &TITLE)
RUN;

/* TRANSFER DF FROM GLMOUT TO LSMOUT33 FOR CI CALCULATIONS */

DATA GLMOUT11;
SET GLMOUT;
IF  SOURCE ='ERROR';
IF NNAME='LAUCT' OR
 NNAME='LAUCI' OR
 NNAME='LCMAX';
/* KEEP NNAME  SOURCE  DF; */
%SORTDS(GLMOUT11, NNAME)
RUN;

/* CALCULATE T AND 90% CI FOR LOG-TRANSFORMED DATA */
%LSMFILE(LSMOUT,TRT,2,LAUCT,LAUCI,LCMAX, , , ,NNAME,OR)
RUN;

%MERGMULT(2,LSMOUT,GLMOUT11, , ,LLSMDAT,NNAME)
RUN;

*****************************************;
data estimates;
  set estimates;

  NNAME = dependent;

  keep NNAME estimate stderr;
run;

proc sort data=estimates;
  by nname;
run;

proc sort data=llsmdat;
  by nname;
run;

data llsmdat;
  merge llsmdat(in=a)
        estimates(in=b);
  by nname;
  if a;
run;
```

```
*********************************************;


DATA LLSMDAT;
SET LLSMDAT;
/* FOR 90% CI, P=0.95 */
%CILOG(0.95,2);

%LET TITLE=90% CONFIDENCE INTERVALS ON LOG-TRANSFORMED DATA;
%*PRINT(LLSMDAT, &TITLE)
RUN;


/* STATISTICS ON TRT1/TRT2 RATIO */
%SPLITBY(BASE,TRT,2,SUB,AUCT,AUCI,CMAX,TMAX,KE,THALF)
RUN;

%MERGMULT(2,BASE, , , ,RATIODAT,SUB)
RUN;

%RATIOCAL(RATIODAT,2,AUCT,AUCI,CMAX,TMAX,KE,THALF)
RUN;

DATA TCDAT;
SET NEWCONC;
KEEP TRT TIME CONC;
%LET BY=TRT TIME;
%SORTDS(TCDAT, &BY)
RUN;

/* CALCULATE MEAN BLOOD LEVEL AT EACH TIME POINT */
TITLE "&TITLE2";
%MEANCAL(TCDAT, CONC, TRT TIME, CMEANOUT)
RUN;
%*PRINT(CMEANOUT, CMEANOUT)
RUN;

DATA CMEANOUT;
SET CMEANOUT;
DROP _TYPE_ _FREQ_ ;

%TRANSPOS(CMEANOUT, CMEAN, CONC, TRT TIME)
RUN;
%*PRINT(CMEAN, CMEAN)
RUN;

DATA CMEAN;
SET CMEAN;
RENAME COL4=MEAN
 COL5=SD;
DROP _NAME_ COL1 COL2 COL3;
%*PRINT(CMEAN, &TITLE1)



%SPLITBY(CMEAN,TRT,2,TIME,MEAN,SD,X,X,X,X)
```

```
RUN;

%MERGMULT(2,CMEAN, , , ,CMEANRAT,TIME)
RUN;
%*PRINT(CMEANRAT,CMEANRAT)
RUN;

%RATIOCAL(CMEANRAT,2,MEAN,X,X,X,X,X)
RUN;
DATA CMEANRAT;
SET CMEANRAT;
DROP TRT;
%*PRINT(CMEANRAT, &TITLE2)
RUN;

%SORTDS(CMEANRAT, TIME)
RUN;

%LET BY=TRT;
%SORTDS(BASE, &BY)
RUN;



%MACRO MEANCAL(DSN, VARN, BY, MEANOUT);
        PROC MEANS DATA=&DSN NOPRINT;
        VAR &VARN;
        BY &BY;
        OUTPUT OUT=&MEANOUT;
%MEND MEANCAL;


%MACRO univCAL(DSN, VARN, BY, MEANOUT);
        PROC univariate DATA=&DSN NOPRINT;
        VAR &VARN;
        BY &BY;
        OUTPUT OUT=&MEANOUT median=median;
%MEND univCAL;


/* CALCULATE MEAN PHARMACOKINETIC PARAMETERS */
%MEANCAL(BASE,AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI
LCMAX,TRT,PARMETER)
RUN;


***** TMAX - MEDIAN DP ********;
%univCAL(BASE,TMAX,TRT,PARMETERtmax)
RUN;


data parmeter;
  merge parmeter

  by trt;
run;
```

```
data parmeter(drop=median);


  if  STAT  = "MEAN" then tmax = median;
  if _STAT_ = "STD" then tmax = .;  ** for median tmax, no SD or CV **;
run;


%LET TITLE=SUMMARY OF PHARMACOKINETIC PARAMETERS;
%*PRINT(PARMETER, &TITLE)
RUN;

DATA PARM;
SET PARMETER;
DROP _TYPE_ _FREQ_ ;

PROC TRANSPOSE DATA=PARM OUT=TRSPARM;
VAR AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI LCMAX;
BY TRT;
RUN;
DATA TRSPARM;
SET TRSPARM;
RENAME _NAME_=NNAME;

%LET BY=NNAME TRT;
%SORTDS(TRSPARM, &BY)
RUN;


***DEV MARCH 23 07**:  COMMENT THIS OUT**;
/*

SET TRSPARM;
DROP COL1 COL2 COL3;
RENAME COL4=MEAN
       COL5=SD;
RUN;
*/
*** COL1=N COL2=MIN COL3=MAX COL4=MEAN COL5=STD**;
DATA TRSPARM;
SET TRSPARM;
DROP COL1;
RENAME COL2=MIN COL3=MAX COL4=MEAN
       COL5=SD;
RUN;


%SPLITBY(TRSPARM,TRT,4,NNAME,MEAN,MIN,MAX,SD,X,X)
RUN;


%MERGMULT(2,TRSPARM, , , ,PARMRAT,NNAME)
RUN;


DATA PARMRATS;
```

```
SET PARMRAT;
IF %SETLST(NNAME,OR,AUCT,AUCI,CMAX,TMAX,KE,THALF);
%RATIOCAL(PARMRATS,2,MEAN,X,X,X,X,X)
RUN;
DATA PARMRATL;
SET PARMRAT;
IF %SETLST(NNAME,OR,LAUCT,LAUCI,LCMAX,X,X,X);
%RATIOLOG(PARMRATL,2,MEAN,X,X,X,X,X)
RUN;
%ANTILOG(PARMRATL,2,MEAN,X,X,X,X,X)
RUN;
DATA PKRATIO;
SET PARMRATS PARMRATL;
DROP TRT;

%LET TITLE=TEST MEAN/REFERENCE MEAN RATIO;
%*PRINT(PKRATIO, &TITLE)
RUN;

%ANTILOG(LLSMDAT,2,LSMEAN,X,X,X,X,X)
RUN;

DATA CIDAT;
SET LSMDAT LLSMDAT;
KEEP NNAME %LSMENLST(2,LSMEAN)  STDERR %CILST(2);

DATA CIDAT;
SET CIDAT;
%RE_NAME(2,LSMEAN,LSM)
RUN;

%SORTDS(CIDAT, NNAME)
RUN;
%*PRINT(CIDAT, CIDAT)
RUN;


%RATIOCAL(CIDAT,2,LSM,X,X,X,X,X)
RUN;


** DEV **;
** CALCULATE %CV **;
data cmeanrat;
  set cmeanrat;

  CV1 = round((sd1/mean1)*100,.01);
  CV2 = round((sd2/mean2)*100,.01);
run;

data pkratio;
  set pkratio;

  CV1 = round((sd1/mean1)*100,.01);

run;
```

```
**DEV TEMPORARILY CLOSED ** MARCH 23 07***;
ods listing close;



** sort order of PK parameters **;
data pkratio;
  set pkratio;

  select(nname);
    when('AUCT') ordervar=1;
      when('AUCI') ordervar=2;
      when('CMAX') ordervar=3;
      when('TMAX') ordervar=4;
      when('KE') ordervar=5;
      when('THALF') ordervar=6;
      when('LAUCT') ordervar=7;
      when('LAUCI') ordervar=8;
      when('LCMAX') ordervar=9;
      otherwise;
  end;
run;

DATA PKRATIO;
  SET PKRATIO;

  IF NNAME IN("LAUCT","LAUCI","LCMAX") THEN DELETE;
RUN;


proc sort
  data=pkratio;
  by ordervar;
run;


data cidat;
  set cidat;

  select(nname);
    when('AUCT') ordervar=1;
      when('AUCI') ordervar=2;
      when('CMAX') ordervar=3;
      when('LAUCT') ordervar=4;
      when('LAUCI') ordervar=5;

      otherwise;
  end;
run;

proc sort
  data=cidat;
  by ordervar;
run;
```

```
DATA cidat;
  SET cidat;

  IF NNAME IN("AUCT","AUCI","CMAX") THEN DELETE;
RUN;


data pkratio;
  set pkratio;

  if nname="AUCT" then units="&aucunit";
  if nname="AUCI" then units="&aucunit";
  if nname="CMAX" then units="&cmaxunit";
  if nname="TMAX" then units="&timeunit";
  if nname="KE" then units="&timeunit.-1";
  if nname="THALF" then units="&timeunit";
run;




data rootmse;
  set fitstat(keep=dependent rootmse);

  if dependent = "LAUCT" then ordervar=1;
  else if dependent="LAUCI" then ordervar=2;


  if dependent in("LAUCT","LAUCI","LCMAX") then output;
run;

proc sort
  data=rootmse;
  by ordervar;
run;



DATA AUCDAT;
SET BASE;
KEEP SUB TRT AUCRATIO;
PROC SORT DATA=AUCDAT;
BY TRT SUB;
RUN;


/* PROC MEANS ON AUCT/AUCI RATIOS */
PROC MEANS DATA=AUCDAT noprint MAXDEC=2 FW=9;
VAR AUCRATIO;
BY TRT;
OUTPUT OUT=AUCRATIO;
TITLE 'STATISTICS ON AUCT/AUCI RATIOS';
RUN;


PROC TRANSPOSE DATA=aucratio OUT=aucratio1;
```

```
VAR aucratio;
BY TRT;
RUN;

data aucratio1;
  length treat $12.;
  set aucratio1;

  rename col1=no col2=mini col3=maxi col4=avg col5=std;
  if trt=1 then treat="TEST";
  else if trt=2 then treat="REFERENCE";
run;



%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%PRINT(AUCDAT, &TITLE)
RUN;


PROC PRINT DATA=RATIODAT ROUND noobs;
VAR SUB SEQ %RATLST(2,AUCT,AUCI,CMAX,TMAX,KE,THALF);
FORMAT %RATLST(2,AUCT,AUCI,CMAX,TMAX,KE,THALF) 4.2;
TITLE 'TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS';
RUN;


ods listing;

/* PROC MEANS ON TEST/REFERENCE RATIOS */
PROC MEANS DATA=RATIODAT MAXDEC=3 FW=9 noprint;
VAR %RATLST(2,AUCT,AUCI,CMAX,TMAX,KE,THALF);

TITLE 'STATISTICS ON THE TEST/REFERENCE RATIOS';
RUN;


DATA CHECKDAT;
SET BASE;

AUCTO_N=OLDAUCT/NEWAUCT;
AUCIO N=OLDAUCI/NEWAUCI;
CMAXO_N=OLDCMAX/NEWCMAX;
TMAXO_N=OLDTMAX/NEWTMAX;

OUTPUT;
KEEP SUB TRT PER SEQ AUCTO_N AUCIO_N CMAXO_N TMAXO_N;
LABEL AUCTO N='AUCT';
LABEL AUCIO_N='AUCI';
LABEL CMAXO_N='CMAX';
LABEL TMAXO_N='TMAX';

%LET TITLE=RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS;
%PRINT(CHECKDAT, &TITLE)
RUN;
```

```
%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%*PRINT(AUCRATIO, &TITLE)
RUN;

/* GOPTIONS DEVICE=EGAL; */     /* GOPTION #1 */
/* GOPTIONS DEVICE=FX85; */     /* GOPTION #2 */
/* GOPTIONS DEVICE=HPLJS2; */   /* GOPTION #3 */
/* GOPTIONS GACCESS='SASGASTD>LPT2:'; */  /* GOPTION #4 */
* GOPTIONS RESET=ALL DEVICE=WIN TARGETDEVICE=WINPRTM ftext=arial; /*
GOPTION
#5 */

ods rtf close;


ods rtf file="&odsfile1" style=mystyle1 bodytitle;

TITLE "MEAN PLASMA CONCENTRATIONS";
proc report data=cmeanrat nowd split='~' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column time ("Test (n=&testsub)" mean1 cv1)
         ("Reference (n=&refsub)" mean2 cv2)
             ("Ratio" rmean12);

  define time /order format=8.2 spacing=2 "Time (hr)";
  define mean1 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv1 /format=8.2 spacing=2 "CV%";
  define mean2 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv2 /format=8.2 spacing=2 "CV%";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;


footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS";
proc report data=pkratio nowd split='\' box

                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
         ("Reference" mean2 cv2 min2 max2)
             ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1   /format=8.2 spacing=2 "CV%";
  define min1  /format=8.2 spacing=2 "Min";
  define max1  /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
```

```
  define cv2   /format=8.2 spacing=2 "CV%";
  define min2  /format=8.2 spacing=2 "Min";
  define max2  /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

TITLE "LSMEANS AND 90% CONFIDENCE INTERVALS";
proc report data=cidat nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column nname ("Least Squares Geometric Mean" lsm1 lsm2)
         ("Ratio" rlsm12)
             ("90% Confidence Intervals" lowci12 uppci12);

  define nname /format=$12. spacing=2 "Parameter";
  define lsm1  /format=8.2 spacing=2 "Test";
  define lsm2 /format=8.2 spacing=2 "Reference";
  define rlsm12 /format=8.2 spacing=2 "(T/R)";

  define uppci12 /format=8.2 spacing=2 "Upper";
run;


TITLE "ROOT MEAN SQUARE ERROR";
proc report data=rootmse nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column dependent rootmse;

  define dependent /format=$12. spacing=2 "Parameter";
  define rootmse /format=8.4 spacing=2 "RMSE";

run;


TITLE "STATISTICS ON AUCT/AUCI RATIOS";
proc report data=aucratio1 nowd split='\' box
  style(header)={background=lightorange
                 foreground=black}
  style(column)={background=white
                 foreground=black};

  column treat no avg mini maxi;

  define treat /format=$12. spacing=2 "Treatment";
  define no /format=8. spacing=2 "n";
  define avg /format=8.2 spacing=2 "Mean";
  define mini /format=8.2 spacing=2 "Minimum";
  define maxi /format=8.2 spacing=2 "Maximum";
run;
```

```
ods rtf close;


filename concplot "&plotfile";

/*
goptions reset=all
         device=cgmof97p
         gsfname=concplot
         gsfmode=replace
         ftext=swiss
         rotate=portrait
           targetdevice=winprtm;
*/

goptions reset=all device=png ftext="Arial" htext=12pt gsfname=concplot
gsfmode=replace



TITLE2 "&TITLE3";
TITLE3 "&TITLE4";
TITLE4 "&TITLE5";
TITLE5 "&TITLE6";
FOOTNOTE1 "&FOOTNOT1";

SYMBOL1 C=RED I=JOIN V=dot  width=0.5 h=0.5;
SYMBOL2 C=BLUE I=JOIN V=SQUARE width=0.5 h=0.5;

AXIS1 label=(a=90 "&label1");

PROC GPLOT DATA=CMEAN UNIFORM;
PLOT MEAN*TIME=TRT / FRAME vaxis=axis1;
LABEL MEAN=("&LABEL1") TIME="&LABEL2";
RUN;
TITLE1;
TITLE2;
TITLE3;
TITLE4;
TITLE5;
TITLE6;

FOOTNOTE1;
FOOTNOTE2;
FOOTNOTE3;
LABEL;
QUIT;
```

4.4.3 Steady State Study Output

MEAN PLASMA CONCENTRATIONS

	Test (n=36)		Reference (n=36)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	2846.19	21.91	2762.55	19.59	1.03
0.50	3224.38	21.53	3092.31	22.87	1.04
1.00	3693.82	22.27	3526.46	22.05	1.05
1.50	3825.19	19.86	3809.57	16.56	1.00
2.00	3814.78	18.84	3839.42	16.16	0.99
2.50	3906.63	20.74	3926.02	16.34	1.00
3.00	3913.26	20.61	3973.19	18.06	0.98
3.50	3810.29	20.85	3850.67	17.09	0.99
4.00	3759.08	21.01	3770.86	17.86	1.00
5.00	3547.53	21.14	3594.22	17.55	0.99
6.00	3159.40	19.79	3236.55	18.01	0.98
8.00	2956.94	20.19	3014.73	17.86	0.98
12.00	2973.46	23.38	2949.66	18.69	1.01
24.00	2721.77	22.52	2769.43	19.99	0.98

ARITHMETIC MEANS AND RATIOS

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	73900.75	19.78	36124.83	100495.2	74237.17	16.67	45409.36	95812.98	1.00
AUCI	ng hr/mL	2597.309	22.06	1153.07	3817.64	2571.232	19.15	1508.44	3514.26	1.01
CMAX	ng/mL	4245.732	19.46	2172.74	5719.07	4248.888	16.44	2614.36	5693.44	1.00
TMAX	hr	2.500	.	0.50	12.00	3.000	.	0.50	5.00	0.83
KE	hr-1	.	.	.	.	.	.	.	.	.
THALF	hr	.	.	.	.	.	.	.	.	.

* Tmax values are presented as median, range.

LSMEANS AND 90% CONFIDENCE INTERVALS

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	72353.81	73067.29	0.99	95.84	102.31
LAUCI	2528.97	2519.91	1.00	95.61	105.35

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LCMAX	4160.77	4178.41	1.00	95.49	103.84

ROOT MEAN SQUARE ERROR

Parameter	RMSE
LAUCT	0.0818
LAUCI	0.1216
LCMAX	0.1049

STATISTICS ON AUCT/AUCI RATIOS

Treatment	n	Mean	Minimum	Maximum
TEST	36	28.67	25.78	35.42
REFERENCE	36	29.07	25.91	34.85

NOTE TO THE PM: BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE FIRM ONLY AFTER ACCEPTABLE OF OSI INSPECTIONS OF THE CLINICAL AND ANALYTICAL SITES

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 207631

APPLICANT: ANI Pharmaceuticals

DRUG PRODUCT: Nilutamide Tablets, 150 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan Stier, Ph.D. R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 207631

Reviewer: Park, Eunjung **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Nilutamide Tablets, 150 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
24083	6/18/2014	Bioequivalence Study (REGULAR)	Steady State BE Study	1	1	Edit	Delete
				Total:	1		

DIVISION OF BIOEQUIVALENCE
DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	207631
Drug Product Name	Nilutamide Tablets
Strength (s)	150 mg
Applicant Name	ANI Pharmaceuticals, Inc.
Applicant Address	210 Main Street West, Baudette, MN 56623
US Agent Name and the mailing address	Ellen Camos, Director, Regulatory Affairs 210 Main Street West, Baudette, MN 56623
US Agent's Telephone Number	(b) (6) 218-634-3638
US Agent's Fax Number	888-519-0459
Original Submission Date(s)	June 18, 2014
Submission Date(s) of Amendment(s) Under Review	September 25, 2014 – Dissolution Acknowledgement
First Generic	Yes
Reviewer	Nabeel Babaa, Pharm.D.
OVERALL DISSOLUTION REVIEW RESULT	**ADEQUATE**

EXECUTIVE SUMMARY

This is a review of the dissolution method and/or specification acknowledgement from the firm. The firm has accepted the following FDA-recommended dissolution method and specification(s).

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT (b) (4)

RECOMMENDATIONS

From a bioequivalence point of view, the firm has met the requirements for in-vitro dissolution testing. The dissolution testing section of the application is adequate and we have no further questions at this time.

DISSOLUTION COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 207631

APPLICANT: ANI Pharmaceuticals, Inc.

DRUG PRODUCT: Nilutamide Tablets, 150 mg

The Division of Bioequivalence II (DBII) has completed its review of your submission acknowledged on the coversheet and has no further questions at this time. We acknowledge that you will conduct the dissolution testing of your test product using the following FDA-recommended dissolution method and specification:

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT (b) (4)

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Completed Assignment for 207631 ID: 24241

Reviewer: Babaa, Nabeel **Date Completed:**
Verifier: Mahadevan, Chitra **Date Verified:** 25SEP2014
Division: Division of Bioequivalence
Description: Diss ack

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
24241	9/25/2014	Dissolution Data (REGULAR)	Dissolution Acknowledgement	0	0
				Total:	0

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

/s/

NABEEL BABAA
09/25/2014

CHITRA MAHADEVAN
09/25/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	207631
Drug Product Name	Nilutamide Tablets
Strength (s)	150 mg
Applicant Name	ANI Pharmaceuticals, Inc.
Applicant Address	210 Main Street West, Baudette, MN 56623
Contact Name and the mailing address	Ellen Camos, Director, Regulatory Affairs 210 Main Street West, Baudette, MN 56623 Email: ellen.camos@anipharmaceuticals.com
Contact's Telephone Number	(b) (6) 218-634-3638
Contact's Fax Number	888-519-0459
Original Submission Date(s)	06/18/2014
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Yue Zhang, Ph.D.
Dissolution Method	**ADEQUATE**
OVERALL REVIEW RESULT	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The reference listed drug (RLD) for this ANDA is COVIS Pharma SARL's Nilandron® (nilutamide) Tablets, 150 mg (NDA020169, approved: April 30, 1999)[1].

There is no USP or FDA recommended dissolution method for this product. However, the FDA online dissolution database entry for Nilutamide Tablets recommends applicants to develop a dissolution method. The firm conducted acceptable dissolution testing using own dissolution method [900 mL of 0.54% SLS in water using USP apparatus II (paddle) at 50 rpm]. However, the firm's proposed specification [NLT (b) (4)] for the test product is not acceptable. Based on the data submitted, the Division of Bioequivalence II (DB II) recommends a more appropriate specification of NLT (b) (4) The firm should indicate if it accepts FDA-recommended dissolution specification.

The analytical method validation reports for dissolution (VAD-TP-0201-00, by (b) (4) and transfer report TR-TP-0201-01 to ANI Pharmaceuticals) are located in Module 3.2.P.5.3.

The *in vitro* dissolution testing is **Inadequate.**

[1] Per Orange Book
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020169&TABLE1=OB_Rx

II. DISSOLUTION REVIEW

II.1 Submission Content Checklist

Information	YES	NO	N/A
Is there a posted dissolution method on the FDA website?	☐	☒	☐
Did the firm use the above method?	☐	☐	☒
Is there a USP dissolution method?	☐	☒	☐
Did the firm use the USP dissolution method?	☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?	☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method?	☒	☐	☐
Did the firm submit dissolution method validation?	☒	☐	☐

Note: The analytical method validation reports for dissolution (VAD-TP-0201-00, by (b) (4) and transfer report TR-TP-0201-01 to ANI Pharmaceuticals) are located in Module 3.2.P.5.3

II.2 Dissolution Method As Posted on the FDA Website

A. External Dissolution Database

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Nilutamide	Tablet			Develop a dissolution method			05/20/2009

Note: There is a control document #08-0396 regarding to develop a dissolution method for Nilutamide Tablet, 150 mg[2].

B. Internal Dissolution Database

No record found

II.3 USP Method

No record found

[2] In OGD Control Document Tracking database, Control#08-0396: \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0396.pdf

II.4 NDA Method

Not to be released under FOIA

In NDA020169 the innovator used the following method and specifications for dissolution testing[3]:

2 OPERATING CONDITIONS

(b) (4)

[redacted]

[3] In DARRTS, NDA020169, ANRPT-13/New/Annual Report, 0000(88), dated 11/17/2009. Module 3.2.P.5.2, and Module 3.2.P.5.1.

Specifications:

II.5 Summary of In Vitro Dissolution Data

Dissolution Conditions	**Apparatus:**	Apparatus II (Paddles)
	Speed of Rotation:	50 rpm
	Medium:	5.4 g/L[4] Sodium Lauryl Sulfate in water
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	Not Less Than (NLT)	(b) (4)
Dissolution Testing Site (Name, Address)	ANI Pharmaceuticals, Inc., 210 Main Street West, Baudette, MN 56623	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Dt.) (Reference – Exp. Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
Study Report #: N/A	05/14/13	Nilutamide Tablets Batch No.: C-0404-31 Mfg Date: April 9, 2013	150 mg Tablet	12	Mean (%)	38	67	85	96	95	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	9	6	4	2	3	
Study Report #: N/A	05/13/14	Nilandron® (Nilutamide Tablets) Batch No.:2AL3A Exp. Date: Mar 2015	150 mg Tablet	12	Mean (%)	35	66	81	89	93	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	8	8	6	4	3	

[4] 0.54%

Dissolution Method SOP effective at the time of testing (Yes/No)	Yes
Were the drug product units pooled during the dissolution testing (Yes/No)?	No
Was the dissolution testing conducted on the bio-batch?	Yes (test: Batch# C-0404-31; reference: 2AL3A)
Age of the test product at the time of dissolution testing.	~ 1 month
Was the reference product expired at the time of dissolution testing (Yes/No)	No
Comments on the variability of the dissolution data	Acceptable (%CV <10 for all sample points)
For two-stage dissolution testing, comment on the method of medium change from acid stage to buffer stage.	N/A

Note:
The study report for dissolution testing is located in module 3.5.P.5.4 (Batch Analyses).
In the dissolution summary table, the testing dates were 5/14/2013 and 5/13/2014, when the firm conducted dissolution study according to procedure (b) (4) The current procedure (b) (4)

Dissolution Data:

Table 1. Nilutamide Tablets, 150 mg, Lot No. C-0404-31					
	% Nilutamide Dissolved				
Tablet	10 min	20 min	30 min	45 min	60 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	**38**	**67**	**85**	**96**	**95**
Min	(b) (4)				
Max					
%RSD	9	6	4	2	3

Table 2. Nilandron Tablets, 150 mg, Lot No. 2AL3A					
	% Nilutamide Dissolved				
Tablet	10 min	20 min	30 min	45 min	60 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	**35**	**66**	**81**	**89**	**93**
Min	(b) (4)				
Max					
%RSD	8	8	6	4	3


(b) (4)

II. Reviewer's Comments for Dissolution Testing

1. There is no USP or FDA recommended method available for this product. The firm developed new dissolution method and specifications for their product Nilutamide Tablets, as per recommendation in the FDA online dissolution database entry for Nilutamide Tablets:

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT (b) (4)

2. The original NDA 020169 used a different dissolution method (b) (4) (b) (4) please see Section II.4).

3. In control document #08-936, the DBE recommended "*the firm* (b) (4) *develop a dissolution method for its Nilutamide Tablets, 150 mg,* (b) (4) *Apparatus II (50* (b) (4) (b) (4) (b) (4) In addition, the firm (b) (4) was asked to conduct dissolution testing comparing the test and RLD products using the NDA method (b) (4)

(b) (4)

(b) (4)

4. The firm did not submit dissolution data comparing test and reference product using NDA method [redacted] (b) (4) After consulting with DB II dissolution focal point Dr. Loice Kikwai, there is no need to ask the firm to repeat dissolution testing with the NDA method, as firm's proposed dissolution method is suitable (please see attached email communication).

5. The firm conducted acceptable dissolution testing using above newly developed method. However, based on submitted data, the release of the test product reached over [redacted] (b) (4) Therefore, the firm proposed specification of NLT [redacted] (b) (4) is too liberal to have discriminatory power. The DB II recommends a data-driven specification of NLT [redacted] (b) (4) The firm should indicate if it accepts above FDA-recommended dissolution specification.

4. The firm submitted an analytical method validation report for dissolution of Nilutamide Tablets (VAD-TP-0201-00, by [redacted] (b) (4) and transfer report TR-TP-0201-01 to ANI Pharmaceuticals; located in Module 3.2.P.5.3).

III. Deficiency Comment for Dissolution Testing

The firm's proposed dissolution specification is not acceptable. Based on the data submitted, the DB II recommends following dissolution method and specification:

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT [redacted] (b) (4)

The firm should indicate if it accepts above FDA-recommended dissolution specification.

IV. Dissolution Recommendations

The *in vitro* dissolution testing conducted by ANI Pharmaceuticals, Inc. on its test product Nilutamide Tablets, 150 mg (Batch# C-0404-31) comparing with COVIS Pharma SARL's Nilandron® (nilutamide) Tablets, 150 mg (lot# 2AL3A) is inadequate due to the deficiency cited above.

V. Attachment: (Consultation to DBE dissolution focal point Dr. Loice Kikwai)

Zhang, Yue

From: Kikwai, Loice
Sent: Wednesday, September 10, 2014 1:39 PM
To: Zhang, Yue
Cc: Chandaroy, Parthapratim
Subject: RE: Question regarding dissolution review ANDA207631

Hello Yue,
Please find below my response to your consult, "My question is whether the new method developed by firm is OK to be reviewed, or should we request the firm to provide data using the original NDA method for comparison?"

Based on the information you provided, review of the Product development report and Control # 08-0396, it is my opinion that the firm's proposed dissolution method is suitable for it test product Nilutamide Tablet 150 mg, therefore it is ok to be reviewed. Please note the specification is too liberal, in my opinion a specification of (b) (4) maybe appropriate.

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in Water
Volume	900 mL
Temperature	37.0 ± 0.5 ° C
Specification	NLT (b) (4)

Because we asked the firm to develop a new method there is no need to ask the firm to repeat dissolution testing with the NDA method.

Please let me know if you have additional questions.

Please note that this is just my opinion. Consult your TL for the final decision.

Thanks,
Loice

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT
(PROCESSED BY BIO-PM)

ANDA: 207631

APPLICANT: ANI Pharmaceuticals, Inc.

DRUG PRODUCT: Nilutamide Tablets, 150 mg

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing using newly developed dissolution method. However, your proposed dissolution specification is not acceptable. Based on the data submitted, the DB II recommends the following dissolution method and specification:

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT (b) (4)

Please indicate if you accept above FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 207631

Completed Assignment for 207631 ID: 24031

Reviewer: Zhang, Yue **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Nilutamide Tablet, 150 mg Dissolution Review

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
24031	6/18/2014	Dissolution Credit (DRGC)	Dissolution Review for Dissolution-Only Credit	1	1
				Total:	1

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

/s/

YUE N ZHANG
09/11/2014

Parthapratim CHANDAROY
09/12/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

OTHER REVIEWS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 6, 2016

TO: Dale Conner, Pharm.D.
Director (acting), Office of Bioequivalence
Office of Generic Drugs

FROM: Kara Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: (b) (4) (b) (4) covering ANDA 207631, Nilutamide Tablets, sponsored by ANI Pharmaceuticals Inc.

Inspection Summary:

At the request of the Office of Generic Drugs (OGD), the Office of Study Integrity and Surveillance (OSIS), in collaboration with the Office of Regulatory Affairs (ORA), conducted an inspection of the clinical and bioanalytical portions of study ANI-NIL.T-07.13-166/127 (b) (4) Based upon the results of this inspection, we recommend that clinical and bioanalytical data in study ANI-NIL.T-07.13-166/127 be accepted for further Agency review.

Study Audited during this Inspection:

Study Number: ANI-NIL.T-07.13-166/127 (ANDA 207631)
Study Title: "Multicenter, Randomized, Two-Period Crossover, Open label, Laboratory-Blind Steady State Bioequivalence Study for Nilutamide 150 mg Tablets (Test Products – ANI Pharmaceuticals, Inc., USA) and Nilandron® 150 mg Tablets

(Reference Product – Sanofi Aventis, USA) after a single daily dose of 150 mg Nilutamide to metastatic prostate cancer male patients"

Study Dates: November 23, 2013 through May 1, 2014
Number of subjects enrolled: 42
Sample Analysis: April 25 through May 5, 2014

OSIS scientist Kara A. Scheibner, Ph.D. and ORA Investigator Lori A. Gioia conducted the inspection of the clinical and bioanalytical portions of study ANI-NIL.T-07.13-166/127 from [redacted]

The clinical portion of the audit included a thorough review of the pharmacy facility, personnel records, sample handling and integrity, protocols, SOPs, subject informed consent, IRB documentation, enrolled subject records, test article accountability, and record retention. [redacted] management and clinical trials staff were also interviewed during the audit.

Please note that while dosing of study drugs and subject monitoring/housing were performed at King Abdullah University Hospital in Irbid, Jordan, all on-site activities during the clinical study were performed [redacted] employees. Study subjects (all metastatic prostate cancer patients) were in-patients of King Abdullah University Hospital, and clinical trial personnel [redacted] traveled to the hospital to direct and conduct investigational product administration and all subject monitoring activities. Study personnel used clinical study protocols and SOPs established [redacted] Reserve samples and study records were stored [redacted] Thus, we consider the clinical operations subject to this inspection to be representative [redacted] practices. Note also that the US Department of State currently restricts travel by US government employees within 10 km of the Syrian border, so the King Abdullah Hospital could not have been visited.

The bioanalytical portion of the audit included a thorough review of facilities and equipment, training records, current bioanalytical SOPs, study records and correspondence, method validation records, and interviews and discussions [redacted] management and staff. The inspection team did not find additional studies suitable for a surveillance assessment of the site.

At the conclusion of the inspection, no Form FDA 483 was issued [redacted] (b) (4)

Recommendation:

Following review of the establishment inspection report, the clinical and analytical data for study ANI-NIL.T-07.13-166/127 were found to be reliable. Therefore, we recommend that data from the clinical and bioanalytical portions of this study be accepted for further Agency review.

Kara Scheibner, Ph.D.
DGDBE, OSIS

Final Classification:

[redacted] (b) (4)

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au/Scheibner
Draft: KAS 06/30/2016
Edit: MFS 07/06/2016; JC 07/07/2016
OSIS file #: 6761
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clincal Sites/Triumpharma, Amman, Jordan
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Bioanalytical Sites/ [redacted] (b) (4)
FACTS: 11596061

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207631

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	**Author:** Heather Strandberg	

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Vikas Arora Team: **Approval Date:**

☐ **PI** ☒ **PII** ☐ **PIII** ☐ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☐ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 207631 **Applicant:** ANI Pharmaceuticals, Inc. **Established Product Name:** Nilutamide Tablets, 150 mg

Basis of Submission (RLD): Nilandron; NDA#020169
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 6/22/2016**

☐ Date last Complete Response (CR) letter was issued -- Date _____

☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

Date of Application 6/18/2014	Original Received Date 6/18/2014	Date Acceptable for Filing 6/18/2014

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Quality 5/11/2016 Date of Acceptable Dissolution 9/25/2014 Date of Acceptable Bioequivalence 7/11/2016 Date of Acceptable Labeling 12/14/2015	If applicable: Date of Acceptable Microbiology _____ Date of Acceptable Clinical Review _____ Date of Acceptable REMS _____
☐	☒	Are consults pending for any discipline?	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed and that all disciplines completed new reviews ☐	
☐	☒	Is there a pending Citizen Petition (CP)?	
☒	☐	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 6/6/2016 Re-evaluation Date: _____	
☒	☐	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed PRIORITY	
Draft Approval/Tentative Approval Letter			
☒	☐	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task	
Review Discipline/Division Endorsements			
☒	☐	Division of Legal and Regulatory Support Endorsement completed, Date 7/13/2016	
☐	☐	Paragraph IV Evaluation completed (if applicable), Date _____	
☒	☐	Quality Endorsement completed, Date 7/14/2016	
☒	☐	Bioequivalence Endorsement completed, Date 7/13/2016	
☒	☐	Labeling Endorsement completed, Date 7/11/2016	
☐	☐	REMS Endorsement (if applicable), Date _____	
RPM Team Leader Endorsement and Action Package Verification			
☒	☐	RPM Team Leader Endorsement completed, Date 7/13/2016	
Final Decision and Letter Sign-off			
☒	☐	Final Decision recommending approval/tentative approval completed, Date 7/15/2016	
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 7/15/2016	
Project Close-Out			
☒	☐	Notify applicant of approval and provide a courtesy copy of the electronically signed letter	
☐	☒	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____	
☒	☐	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information	

This page to be completed by the RPM

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 7/13/2016
Name/Title: HS

Contains GDEA certification: Yes ☒ No ☐	
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Nilandron NDA# 20169 Date Checked 7/13/2016 Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days: Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☐	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER:	
Comments:	
ANDA submitted on 6/18/2014. BOS = Nilandron NDA 20169. PII cert provided. ANDA ack for filing on 6/18/2014 (LO date 8/8/2014). This ANDA is eligible for immediate Full Approval. There are no unexpired patents or exclusivities protecting the RLD. There are no pending CPs for this drug product.	

2. ***Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

3. ***Quality Endorsement by the Office of Pharmaceutical Science***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

4. ***Bioequivalence Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

5. ***Labeling Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

6. ***REMS Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

7. ***RPM Team Leader Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

8. Final Decision

Date: 7/15/2016
Name/Title: cah

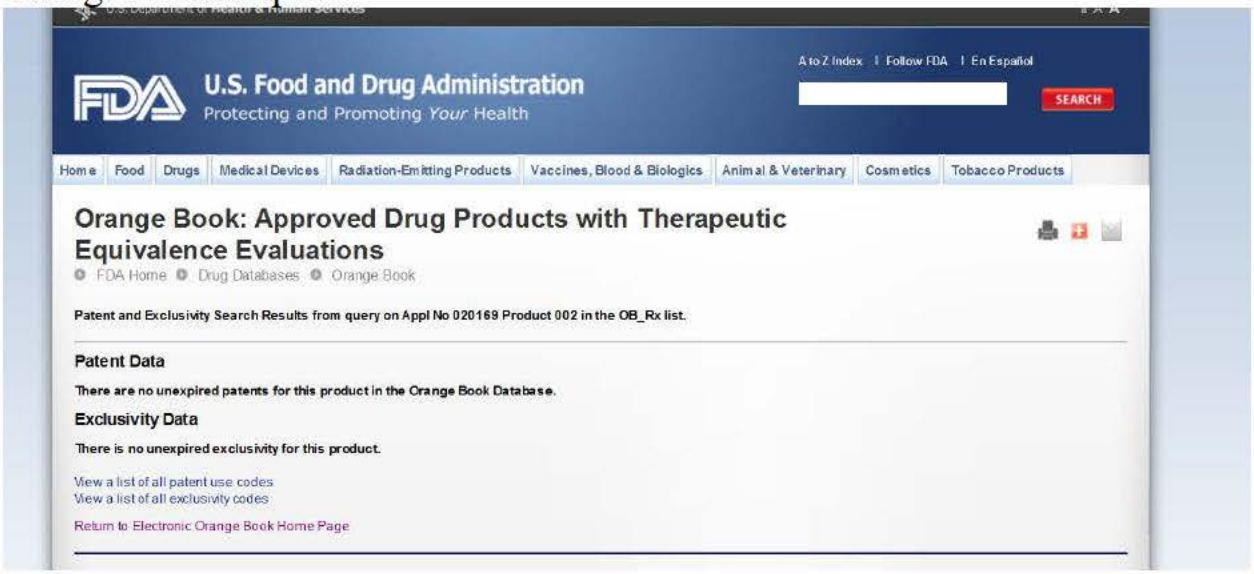
Para.IV Patent Cert: Yes ☐ ☐ ☐ No ☒
Pending Legal Action: Yes ☐ ☐ No ☒
Petition: Yes ☐ No ☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met ☒ Unmet ☐
Press Release Acceptable ☐
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Date PETS checked for first generic drug _____

Comments:
ANDA was submitted and received on 6/18/2014 for Nilutamide. The BOS = Nilandron, NDA 20169, Concordia Pharms Inc. The applicant provided a PII cert. ANDA ack for filing on 6/18/2014 (LO date 8/8/2014). There are no new patents or exclusivities listed in the OBook (7/15/16 search). There are no issues on the OGD Policy Alert list (7/8/16). There is no REMS needed. Dissolution adequate on 9/25/14 - Applicant using FDA method. Bio – Steady state BE study conducted on the 150 mg strength – Consistent with BE guidance recommendations (10/11). Review by Park on 10/11/14 is adequate pending OSIS. No OSIS issues per review by Pokora/Chan 7/11/16. Drug Product review on 5/11/16 is adequate. DMF (b) (4) is adequate 6/15/16. QE completed by Nagavelli on 7/14/16. Labeling is adequate on 12/14/15. Labeling RL endorsement completed by Kwok on 7/11/16. Bio endorsement completed by Stier on 7/13/16. The overall manufacturing inspection recommendation is approve (see screen shots). This ANDA is eligible for immediate Full Approval. There are no unexpired patents or exclusivities protecting the RLD. There are no pending CPs for this drug product.

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Orange Book Report:



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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home › Drug Databases › Orange Book

Patent and Exclusivity Search Results from query on Appl No 020169 Product 002 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/08/2016 02:43:47 PM
To: ellen.camos@anipharmaceuticals.com
CC:
BCC: vikas.arora@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 207631

ANDA 207631

NOTIFICATION -- TARGET ACTION DATE

ANI PHARMACEUTICALS INC
210 MAIN ST WEST
BAUDETTE, MINNESOTA 56623 UNITED STATES
Attention: Ellen Camos

Dear Madam,

This letter is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Nilutamide Tablets, 150 mg.

We acknowledge your response to the complete set of Informational Requests dated March 7, 2016.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our new internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated its comments to the applicant. In that case, the TAD will be met if the last discipline

communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is June 7, 2016.

Please contact your Regulatory Project Manager, Vikas Arora at (240) 402-8884 for an additional status update of your application.

Sincerely,

Vikas Arora
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/08/2015 03:11:54 PM

To: ellen.camos@anipharmaceuticals.com;steven.yang@fda.hhs.gov

CC:

BCC:

Subject: INFORMATION REQUEST - ANDA 207631

Please see attached letter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207631

INFORMATION REQUEST

ANI Pharmaceuticals, Inc.
Attention: Ellen Camos
Director Regulatory Affairs
210 Main Street West
Baudette, MN 56623

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 18, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Nilutamide Tablets, 150 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, (Note for ANDA products: in general the requested date should not exceed 30 days per SOP (b) (4) Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your ANDA.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

The following deficiencies represent Minor deficiencies:

(b) (4) for Nilutamide is found Inadequate. Please consult with your DMF holder and update specifications for the drug substance to include any potential impurities that were not addressed or that may arise from the additional evaluation of the drug substance as requested of the DMF holder. Please also include the names, structures, source or route of formation as well as define whether each impurity is a process impurity or degradation product. In addition, please demonstrate that your method is suitable for analysis and capable of detecting and qualifying these potential impurities.

If you do not submit a complete response by January 8, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently

identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Chemistry
REFERENCE # 198907

If you have any questions, please contact Steven Yang, Regulatory Business Project Manager, at (240) 402-9122.

Sincerely,

Steven Yang -S

Digitally signed by Steven Yang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Yang -S, 0.9.2342.19200300.100.1.1=2000531536
Date: 2015.12.08 15:07:36 -05'00'

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/27/2015 09:20:00 AM
To: ellen.camos@anipharmaceuticals.com
CC: carrie.lemley@fda.hhs.gov, olive.paul@fda.hhs.gov
BCC:
Subject: EASILY CORRECTABLE DEFICIENCY Original ANDA 207631

ANDA 207631

EASILY CORRECTABLE DEFICIENCY
Original ANDA

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623

Attention: Ellen Camos
Director of Regulatory Affairs

Dear Ms. Camos:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 18, 2014 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nilutamide Tablets , 150 mg.

See Attached Labeling Deficiencies.

Provide a complete response to these deficiencies by November 10, 2015. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY

LABEING
REFERENCE # 178539

If you do not submit a complete response by November 10, 2015, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you do not submit a complete response by November 10, 2015, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

Please acknowledge the receipt by sending confirmation to carrie.lemley@fda.hhs.gov.

If you have questions, please contact Carrie Lemley via email at Carrie.Lemley@fda.hhs.gov.

Sincerely,

Carrie Lemley
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

LABELING DEFICIENCIES

Please make the following revisions:

1. Container Label (blister)
    a. [redacted] the established name to read "Nilutamide Tablet" on individual blisters.
    b. Include a bar code to identify each blister if your drug product is for unit dose dispensing.
2. Carton Labeling
    a. Please indicate if the drug product is intended for dispensing [redacted] as unit of use packaging. We note your statement in 2.3.P.2.4, the "product should have the same container closure attributes as that of RLD"; however, please specify whether your container or carton are child resistant. Please note if your product is unit of use, the blister packaging should be child-resistant.
    b. Revise the net quantity statement to read [redacted] "30 (3 x 10) Unit of Use Tablets" as applicable.
3. Prescribing Information
    a. We note you list the starch as [redacted] starch. [redacted]
    b. Consider replacing hyphens with "to" when referencing a range of numbers (e.g., "…15 to 30°C (59 to 86°F)…").
    c. [redacted] package insert and revise the remaining date to reflect the actual revision date.
    d. Description
    Revise the last sentence to read "Each Nilutamide Tablet contains…"
    e. Warnings
    [redacted] the "Interstitial Pneumonitis" heading [redacted] the last sentence "**If symptoms occur…determined if the symptoms are drug related."**
    f. Information for Patients:
    Bold the paragraph beginning "**In clinical trials, 13% to 57% of patients… alleviated by the wearing of tinted glasses.**"
    g. Carcinogenesis, Mutagenesis, Impairment Of Fertility
    Create a new paragraph [redacted] "Nilutamide displayed no mutagenic effects in a variety of in vitro and in vivo tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests)."
    h. Animal Pharmacology and Toxicology
        i. Create a new paragraph with the sentence "Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1–2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis)."
        ii. Create a new paragraph with the sentences "The hepatic and pulmonary adverse effects… P450 reductase in the lungs and liver of rats and humans."
    i. How Supplied
    Revise the first sentence to read "Nilutamide Tablets, 150 mg, are…"

4. Structured Product Labeling (SPL)
    a. Revise Inactive Ingredients to accurately reflect ingredients in the product [redacted] (b) (4) SPL data elements states [redacted] (b) (4)
    b. Revise Product Characteristics to reflect description in How Supplied section "white to off-white".
    c. Revise Package Description to read [redacted] (b) (4)

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the last submitted labeling and all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 07/21/2015 02:04:01 PM
To: ellen.camos@anipharmaceuticals.com
CC:
BCC: Bic.Nguyen@fda.hhs.gov, Dat.Doan@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 207631

ANDA 207631

NOTIFICATION -- TARGET ACTION DATE

ANI PHARMACEUTICALS INC
210 MAIN ST WEST
BAUDETTE, MINNESOTA 56623 UNITED STATES
Attention: Ellen Camos

Dear Madam,

Please refer to your Abbreviated New Drug Application (ANDA) dated June 18, 2014, received June 18, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nilutamide Tablets, 150 mg.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. “Communication” for these purposes is a Complete Response, a Tentative Approval, a Final Approval, an Information Request or an Easily Correctable Deficiency.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User

Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is February 26, 2016.

Please contact your Regulatory Project Manager, Vikas Arora at (240) 402-8884 three months prior to your Target Action Date for an additional status update of your application.

Sincerely,

Division of Project Management
Office of Regulatory Operations
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 04/30/2015 12:03:07 PM

To: ellen.camos@anipharmaceuticals.com; steven.yang@fda.hhs.gov

CC:

BCC:

Subject: INFORMATION REQUEST Original ANDA

Please see attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207631

INFORMATION REQUEST
Original ANDA

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623

Attention: Ellen Camos

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 18, 2014 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nilutamide Tablets, 150 mg.

Please respond to the following information request:

A. Deficiencies

1. (b) (4)
2.
3.
4.
5.

6. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. [redacted] (b) (4)

2.

3.

Please provide a response to these deficiencies by May 30, 2015.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
DIVISION OF FILING REVIEW
REFERENCE # 106849

If you have questions, please contact Steven Yang at 240-402-9122 or email at steven.yang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Yang
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Steven Yang -S

Digitally signed by Steven Yang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Yang -S, 0.9.2342.19200300.100.1.1=2000531536
Date: 2015.04.30 12:00:56 -04'00'

BIOEQUIVALENCE AMENDMENT

ANDA 207631

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: ANI Pharmaceuticals, Inc. (b) (6)

ATTN: Ellen Camos FAX: (888) 519-0459

FROM: Vikas Arora FDA CONTACT PHONE: (240) 402-8884

Dear Sir/Madam:

This facsimile is in reference to the bioequivalence data submitted on June 18, 2014, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nilutamide Tablets, 150 mg.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

BIOEQUIVALENCE DEFICIENCY

ANDA: 207631

APPLICANT: ANI Pharmaceuticals, Inc.

DRUG PRODUCT: Nilutamide Tablets, 150 mg

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing using newly developed dissolution method. However, your proposed dissolution specification is not acceptable. Based on the data submitted, the DB II recommends the following dissolution method and specification:

Apparatus	II (Paddle)
Speed of Rotation	50 rpm
Medium	0.54% Sodium Lauryl Sulfate in water
Volume	900 mL
Temperature	37.0 ± 0.5 °C
Specification	NLT (b) (4)

Please indicate if you accept above FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

XIAOJIAN JIANG on behalf of ETHAN M STIER
09/23/2014

OSI Consult Request for Biopharmaceutical Inspections	
Date	9/23/2014
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	OGD/DB2
Project Manager	Babaa, Nabeel
Application Type	PEPFAR? ☐ Yes ☒ No
	☐ NDA ☐ BLA ☒ ANDA
Application Number	207631
Drug Product	Nilutamide Tablets
Sponsor Name	ANI Pharmaceuticals Inc.
Sponsor Address	210 Main Street West, Baudette, MN 56623
US Agent (if applicable)	Ellen Camos
US Agent Address	210 Main Street West, Baudette, MN 56623
Electronic Submission	☒ Yes ☐ No
PDUFA Due Date Action Goal Date OSI Review Requested By	N/A 03/23/2014 Ethan M. Stier, Ph.D., R.Ph.

Inspection Request Detail (All fields should be fill out completely)				
Study #1				
Study Number	ANI-NIL.T-07.13-166/127			
Study Title	Multicenter, Randomized, Two-Period Crossover, Open label, Laboratory-Blind Steady State Bioequivalence Study for Nilutamide 150 mg Tablets (Test Product- ANI Pharmaceuticals, Inc., USA)- and Nilandron® 150 mg Tablets (Reference Product- Sanofi Aventis, USA) after a single daily dose of 150 mg Nilutamide to metastatic prostate cancer male patients			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)
☒ Inspection Request - Clinical Site			☒ Inspection Request - Analytical Site	
Facility #1 Name: King Abdullah University Hospital, Address: PO Box 630001, Irbid 22110, Jordan (Tel) (Fax)			(b) (4)	
Clinical Investigator: Dr. Rami Al-Azab, M.D (email)			(b) (4)	
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)			Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)	
Check one: ☒ Routine inspection ☐ For cause			Check one: ☒ Routine inspection ☐ For cause	
(please include specific review concerns or items to be addressed during the inspection in the appendix below)				
☐ Study Report: (location, eg., 5.3.1.2)			☐ Validation Report: (eg., 5.3.1.2) ☐ Bioanalytical Report: (eg., 5.3.1.4)	

Study #2				
Study Number				
Study Title				
Study Type	☐ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)

☐ Inspection Request - Clinical Site	☐ Inspection Request - Analytical Site
Facility #1 Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility #1 Name: (or indicate if same as above) Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)	Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)
Check one: ☐ Routine inspection ☐ For cause	Check one: ☐ Routine inspection ☐ For cause
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	
☐ Study Report: (location, eg., 5.3.1.2)	☐ Validation Report: (eg., 5.3.1.2) ☐ Bioanalytical Report: (eg., 5.3.1.4)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection
Confirmed with Nicola Fenty-Stewart via email on 9/10/14 that there is no inspection history for the clinical site. The last inspection for the analytical site was in [redacted] (b) (4) final classification was VAI. We are thus requesting a routine inspection of both the clinical and analytical sites. Please note that this is for a first generic application.

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

/s/

NABEEL BABAA
09/23/2014

ETHAN M STIER
09/23/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 207631

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: ANI Pharmaceuticals, Inc.
ATTN: Ellen Camos

(b) (6)

FAX: (888) 519-0459

FROM: Nabeel Babaa

FDA CONTACT PHONE: (240) 402-3880

Dear Sir/Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated June 18, 2014, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nilutamide Tablets, 150 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
BIOEQUIVALENCE

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Vikas Arora, at (240) 402-8884.

We have completed our review, as amended, and have the following comments:

BIOEQUIVALENCE

1. Please submit the raw numerical data of sample analysis such as HPLC results including peak area of samples and internal standards for all subjects.

2. Please submit the following SOPs; Bioanalytical Method Development (b) (4) Bioanalytical Method Validation (b) (4) Standard Practices for Chromatographic Analysis (b) (4) Handling of Standard Curve and QC Results (b) (4) and incurred sample analysis.

3. LTSS was reported as 207 days at -70°C in bio-summary table but the reviewer cannot locate the LTSS data in the validation report. Please provide the LTSS data for 207 days at -70°C which cover the sample storage period of 151 days.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ETHAN M STIER
09/23/2014

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 207631 APPLICANT: ANI Pharmaceuticals
DRUG: Nilutamide Tablets, 150 mg DATE OF SUBMISSION:6/18/2014

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,MaPP 5240.3 & GDUFA). At least one of the criteria must be met to receive Expedited Review Status:

1. ☐ **PUBLIC HEALTH NEED**. Events that affect the availability of a drug for which there is no alternative

2. ☐ **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. **AGENCY NEED.**
   a) ☐ Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) ☐ Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) ☐ Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) ☐ Request for approval of a strength that was previously tentatively approved (To be used in those cases where l80-day generic drug exclusivity prevented full approval of all strengths).
   e) ☐ MaPP 5240.3 conditions.

4. ☒ **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☐ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #

ENTER FORM INTO DAARTS DATE

Paste Email Copy Below:

Chen, Peter

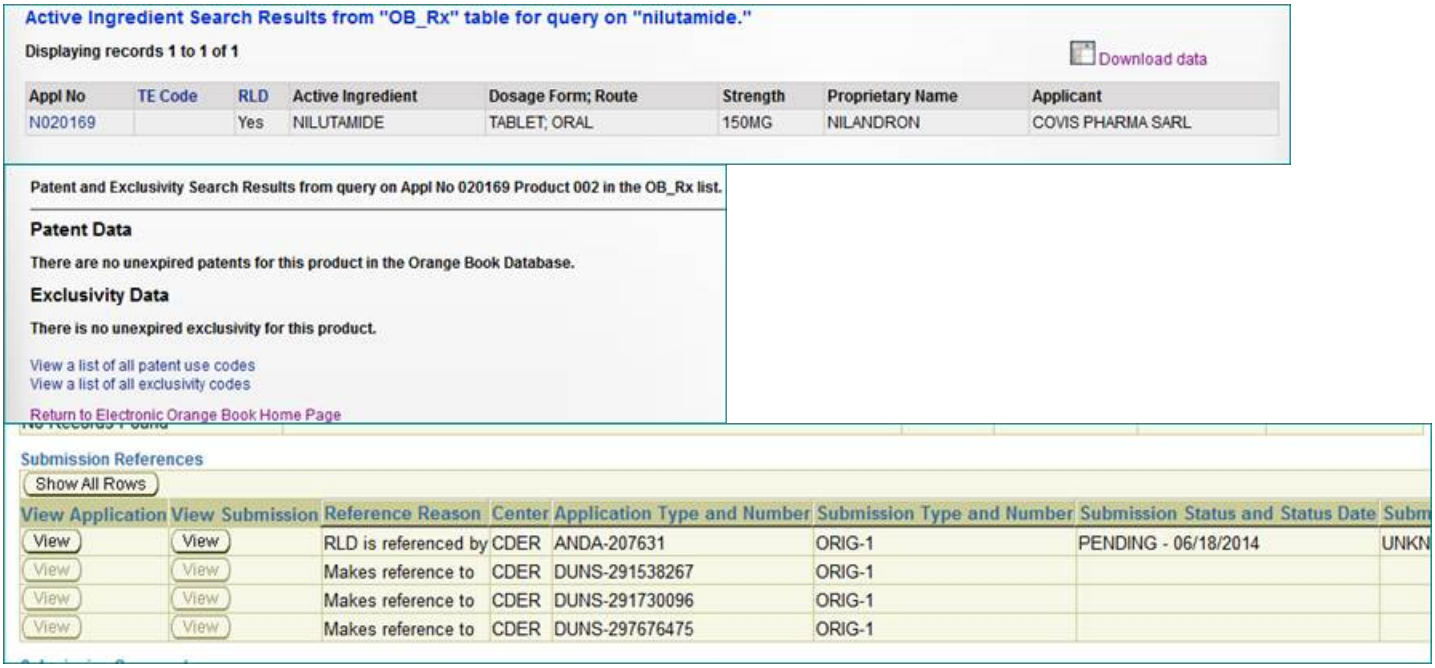
From: Vo, To-Linh
Sent: Friday, July 18, 2014 9:25 AM
To: Chen, Peter
Cc: Polifko, Susan
Subject: RE: Expedited Review Requested for ANDA 207631

Hi Peter,

Yes, I concur that expedited review should be granted to ANI's ANDA 207631 for Nilutamide tablet, 150 mg. It meets criteria per MaPP 5240.3, as there are no approved generics based the RLD 020169. There are currently no blocking patents or exclusivities for the RLD.

Thanks,
Linh

RLD: Nilandron- N20169



Active Ingredient Search Results from "OB_Rx" table for query on "nilutamide."

Displaying records 1 to 1 of 1

Download data

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020169		Yes	NILUTAMIDE	TABLET; ORAL	150MG	NILANDRON	COVIS PHARMA SARL

Patent and Exclusivity Search Results from query on Appl No 020169 Product 002 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

Submission References

Show All Rows

View Application	View Submission	Reference Reason	Center	Application Type and Number	Submission Type and Number	Submission Status and Status Date	Subm
View	View	RLD is referenced by	CDER	ANDA-207631	ORIG-1	PENDING - 06/18/2014	UNKN
View	View	Makes reference to	CDER	DUNS-291538267	ORIG-1		
View	View	Makes reference to	CDER	DUNS-291730096	ORIG-1		
View	View	Makes reference to	CDER	DUNS-297676475	ORIG-1		

From: Chen, Peter
Sent: Thursday, July 17, 2014 8:29 AM
To: Vo, To-Linh
Subject: Expedited Review Requested for ANDA 207631

Hi Linh,

ANDA 207631 for Nilutamide Tablets, 150 mg has been submitted by Ani Pharmaceuticals, Inc. Expedited review has been requested based on MaPP 5240.3. There are currently no approved generics based the RLD 020169. There are currently no blocking patents or exclusivities for the RLD. Do you agree that expedited review should be granted?

Thanks,

Peter Chen, R.Ph.
CDR, United States Public Health Service
OGD/Division of Filing Review
P: 240-402-8605

APPEARS THIS WAY ON ORIGINAL

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

/s/

PETER CHEN
08/08/2014

IAIN MARGAND
08/08/2014

ANDA FILING CHECKLIST

(Pre June 20, 2014)

ANDA:	207631
APPLICANT:	ANI Pharmaceuticals, Inc
RELATED APPLICATION(S):	~RELATEDAPPLICATIONS~
DRUG NAME:	**Nilutamide**
DOSAGE FORM:	Tablets, 150 mg
LETTER DATE:	6/18/2014
RECEIVED DATE:	6/18/2014
Type II DMF #:	(b) (4)
Therapeutic Code:	3010310 (Antiandrogens)
Archival Copy:	Gateway

BASIS OF SUBMISSION:

NDA/ANDA:	**NDA 020169**
FIRM:	**COVIS PHARMA SARL**
RLD:	**NILANDRON**
On Cards:	Yes

APPLICATION PROPERTIES

P-IV	☐ Yes ☐ No
EXPEDITED REVIEW REQUEST	☒ Yes
MaPP 5240.1 or 5240.3 or GDUFA	☐ Approved ☐ Denied
FIRST GENERIC Received	☒ Yes ☐ No
Market Availability	☒ Rx ☐ OTC
PEPFAR	☐ Yes ☒ No
PET	☐ Yes ☐ No
Product Type	☐ Small Molecule Drug
USP Drug Product (at time of filing review)	☐ Yes ☒ No

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

RPM:	**Denise McKan** ☒ **Activity**	Div. of Bioequivalence:	**Team 24** ☒ **Activity**
CHEM Team:	**DC3 Team 31** ☒ **FYI**	Dissolution Review:	~DissoTeam~ ☐ **FYI**
CHEM PQRPM:	**Steven Yang** ☒ **FYI**	Division of Clinical Review:	☐ **Activity**
CHEM Team Leader:	Guoping Sun ☐ **No Assignment Needed in DARRTS**	DMF Review Team Leader:	Dave Skanchy ☒ **FYI**
Labeling Team:	**Burhan Nour** ☒ **Activity**	Micro Review:	☐ **Activity**

SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):

Regulatory Reviewer: Date:	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

1. Edit Application Property Type in DARRTS
2. Edit Submission Patent Records
   ☐ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. EER (internal notation: RSB to submit at time of filing)
   ☒ Yes
5. GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee)
   ☒ Yes- (internal notation-if not met contact: cder-om-collection@fda.hhs.gov)
6. DMF Complete Assessment
   ☒ Yes on 7/30/2014

ADDITIONAL COMMENTS REGARDING THE ANDA:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: January 31, 2017
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*: 06/18/2014

APPLICANT INFORMATION

2. Name of Applicant: ANI Pharmaceuticals, Inc

3. Telephone Number *(Include country code if applicable and area code)*: 218.634.3500

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*: 888.519.0459

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*: 210 Main Street West

Address 2 *(Apartment, suite, unit, building, floor, etc.)*:

City: Baudette

State/Province/Region: MN

Country: USA

ZIP or Postal Code: 56623

Email Address: ellen.camos@anipharmaceuticals.com

U.S. License Number if previously issued:

6. Authorized U.S. Agent *(Required for non-U.S. applicants)*

Authorized U.S. Agent Name:

Address 1 *(Street address, P.O. box, company name c/o)*:

Address 2 *(Apartment, suite, unit, building, floor, etc.)*:

City:

State:

ZIP Code:

Telephone Number *(Include area code)*:

FAX Number *(Include area code)*:

Email Address:

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number: 207631

8. Supplement Number *(If applicable)*:

9. Established Name *(e.g., proper name, USP/USAN name)*: Nilutamide Tablets

10. Proprietary Name *(Trade Name) (If any)*:

11. Chemical/Biochemical/Blood Product Name *(If any)*: 5,5-Dimethyl-3-(4-Nitro-3-(trifluoromethyl) phenyl) imidazolidine-2, 4-dione

12. Dosage Form: Tablet

13. Strengths: 150 mg

14. Route of Administration: Oral

15. Proposed Indication for Use: indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2)

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☑ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☑ No

If yes, provide the Orphan Designation number for this indication:

Contin. Page for #15

APPLICATION INFORMATION

16. Application Type *(Select one)*: ☐ New Drug Application (NDA) ☐ Biologics License Application (BLA) ☑ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type: ☐ 505 (b)(1) ☐ 505 (b)(2)

18. If a BLA, identify the type: ☐ 351 (a) ☐ 351 (k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is the basis for the submission.
Name of Drug: Nilandron® (Nilutamide Tablets) Application Number of Relied Upon Product: 020169
Indicate Patent Certification(s): ☐ P1 ☑ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

21. Submission *(Select one)*: ☑ Original ☐ Labeling Supplement ☐ CMC Supplement ☐ Efficacy Supplement ☐ Annual Report ☐ Product Correspondence ☐ REMS Supplement ☐ Postmarketing Requirements or Commitments ☐ Periodic Safety Report ☐ Other *(Specify)*: _____

PSC Publishing Services (301) 443-6740 EF

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

32. Typed Name and Title of Applicant's Responsible Official	33. Date *(mm/dd/yyyy)*
Ellen Camos, Director of Regulatory Affairs	06/16/2014

34. Telephone Number *(Include country code if applicable and area code)*	35. FAX Number *(Include country code if applicable and area code)*	36. Email Address
(b) (6)	888.519.0459	ellen.camos@anipharmaceuticals.com

37. Address of Applicant's Responsible Official

Address 1 *(Street address, P.O. box, company name c/o)*		
210 Main Street West		
Address 2 *(Apartment, suite, unit, buiding, floor, etc.)*		
City	State/Province/Region	
Baudette	MN	
Country	ZIP or Postal Code	
USA	56623	

38. Signature of Applicant's Responsible Official or Other Authorized Official	39. Countersignature of Authorized U.S. Agent
Sign	Sign
Ellen Camos Digitally signed by Ellen Camos DN: c=US, st=Minnesota, l=Baudette, o=ANI Pharmaceuticals, Inc., cn=Ellen Camos, email=ellen.camos@anipharmaceuticals.com Date: 2014.06.14 15:03:39 -04'00'	

MODULE 1: ADMINISTRATIVE

			COMMENT(S)
1.1	1.1.2	**Signed and Completed Application Form (356h)** (Rx / OTC Status) **Select** (original signature) **Electronic, Fillable Copy** (if a signed, scanned copy is provided) **Select** Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING***	Checked
		Form FDA 3794 (PDF) GDUFA **Select**	
1.2	*	**Cover Letter Select** **Is the drug product subject to REMS requirements?** ☐ Yes ☐ No	Checked
	1.2.1	**Form FDA 3674 (PDF)** 42 U.S.C. 282(j)(5)(B) **Select** **Electronic, Fillable Copy** (if a signed, scanned copy is provided) **Select**	Checked
*	*	**Table of Contents** (paper submission only) N/A	
1.3	1.3.1	**Contact/Sponsor/Applicant Information** **1.3.1.2 U.S. Agent Appointment Letter** 21 CFR §314.50(a)(5) **Select** If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided.	
	1.3.2	**Field Copy Certification** 21CFR §314.94(d)(5) **Select** (Original Signature)	
	1.3.3	**Debarment Certification** Generic Drug Enforcement Act (GDEA)/ Other: (no qualifying statement) FD&C Act §306(k), §306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b)) 1. Debarment Certification (original signature) **Select** 2. List of Convictions statement (original signature) **Select**	Checked
	1.3.4	**Financial Certifications** 21 CFR §54 | 21 CFR §54.2(e) | 21 CFR §314.94(13) Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) **Select** Disclosure Statement (Form FDA 3455) **Select**	Checked
	1.3.5	**Patent and exclusivity** **1.3.5.1 Patent Information** 21 CFR §314.94(a)(12) | FD&C Act 505(j)(2)(A)(vii) Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii) 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU☐ PI☐ PII☒ PIII☐ PIV☐ Statement of Notification (21 CFR §314.95 | 505(j)(2)(B))☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? **Select** b. Expiration of Pediatric Exclusivity? **1.3.5.3 Exclusivity Claim** Exclusivity Statement: State marketing intentions? **Yes**	Checked
1.4	1.4.2	**Statement of right of references** 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of LoA received from DMF holders) 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient **Select** 2. Type II DMF# (b) (4) 3. Type III DMF authorization letter(s) for container closure **Select** 4. Type III or IV DMF authorization letter(s) for sterile product sterilization process **Select**	Checked
1.12	1.12.4	**Request for Comments and Advice** – Proprietary name requested **Select** If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes **Select** 2. No – contact the firm to submit the request as a separate electronic amendment	
	1.12.11	**Basis for Submission** 21 CFR §314.94(a)(3) NDA#: NDA 020169 Ref Listed Drug: NILANDRON Firm: NOVIS PHARMA SARL	Checked

		ANDA suitability petition required? 21 CFR §10.20 | 21 CFR §10.30 | 21 CFR §314.93 **Select** If Yes, provide petition number and copy of approved petition (21 CFR §314.94(a)(3)(iii)) ANDA Citizen's Petition required? 21 CFR §10.25(a) | 21 CFR §10.30 | 21 CFR §314.122 **Select** If Yes, provide petition number and copy of petition	
	1.12.12	Comparison between Generic Drug and RLD 505(j)(2)(A) | 21 CFR §314.94(a)(4) to (6) 1. Conditions of Use **Select** 2. Active Ingredients **Select** 3. Inactive Ingredients (21 CFR §314.94(a)(9)(ii)) **Select** 4. Route of Administration **Select** 5. Dosage Form **Select** 6. Strength **Select**	Checked
	1.12.14	Environmental Impact Analysis Statement 21 CFR §25.15(d) Environmental Assessment (EA) (21 CFR §25.20) **Select** Environmental Impact Statement (EIS) (21 CFR 25.22) **Select** Claim of Categorical Exclusion (21 CFR §25.30 or 21 CFR §25.31) **Select**	
	1.12.15	Request for Waiver 21 CFR 320.22 | 320.24(b)(6) Request for Waiver of In-Vivo BA/BE Study(ies) **Select**	
1.14	1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 21 CFR 314.94(a)(8)(ii) 1.14.1.1 Draft carton and container labels 4 copies of draft for paper submission only (each strength and container) **Select** 1.14.1.2 Annotated draft labeling text 21 CFR §314.94(a)(8)(iv) Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated **Select** 1.14.1.3 Draft labeling text 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically **Select** 1.14.1.4 Labeling Comprehension Studies Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf	Checked
	1.14.3	Listed Drug Labeling 1.14.3.1 Annotated comparison with listed drug 21 CFR §314.94(a)(8)(iv) 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated **Select** 1.14.3.3 Labeling text for reference listed drug RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label **Select**	Checked

HOW SUPPLIED

Nilutamide Tablets 150 mg are supplied in boxes of 30 tablets. Each box contains (b) (4) (b) (4) Each round, biconvex, white to off-white tablet is debossed with "ANI" and "173" on one side and plain on the other side.

MODULE 2: CTD SUMMARIES

		COMMENT(S)
2.3	Quality Overall Summary (QOS) E-Submission: PDF Select Word Processed, e.g., MS Word Select Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm Question based Review (QbR) Select 2.3.S Drug Substance (Active Pharmaceutical Ingredient) Select 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product Select 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product Oral Solids: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	Checked

		COMMENT(S)
2.7	**Clinical Summary (Bioequivalence)** Model BE Data Summary Tables http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApplicationsforFDAApprovalAbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf ** In addition to the standard tables, see the link above for tables specifically designed for in-vitro binding studies ** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApplicationsforFDAApprovalAbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf E-Submission: PDF Select Word Processed: e.g., MS Word Select 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary Select Table 4. Bioanalytical Method Validation Select Table 6. Formulation Data Select Table 10. Study Information Select Table 11. Product Information Select Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products Select 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro DissolutionSelect (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples Select Table 12. Dropout Information Select Table 13. Protocol Deviation Select Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis Select 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies Select Table 3. Statistical Summary of the Comparative BA Data: 1. Unscaled Average – Table A 2. Reference-scaled Average BE Studies – Tables A and B BE Studies Select Table 16. Composition of Meal Used in Fed Bioequivalence Study Select 2.7.1.4 Appendix Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Select 2.7.4 Summary of Clinical Safety 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Select 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies Select	Checked

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (Active Pharmaceutical Ingredient)

		COMMENT(S)
3.2.S.1	**General Information Select** (Do not refer to DMF) **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	
3.2.S.2	**Manufacturer** **Drug Substance (Active Pharmaceutical Ingredient)** Must correlate to the establishment information submitted in annex to Form FDA 356h 1. Name and Full Address(es) of the Facility(ies) **Select** 2. Contact name, phone and fax numbers, email address **Select** 3. U.S. Agent's Name (if applicable) **Select** 4. Specify function or responsibility **Select** 5. Type II DMF number for API **Select** 6. CFN, FEI, or DUNS number (if available) **Select**	Checked
3.2.S.3	**Characterization Select** Provide the following in tabular format as follows: IUPAC Chemical Name | Code # | Chemical Structure | Process/ Degradation Impurity | Source/ Mechanism http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf	

Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4	3.2.S.4.1	**Specification** Testing specifications and data from drug substance manufacturer(s) **Select**	Checked
	3.2.S.4.2	**Analytical Procedures Select**	
	3.2.S.4.3	**Validation of Analytical Procedures** (API that is USP or reference made to DMF, **MUST** provide verification of USP or DMF procedures) **Select** 1. Spectra and chromatograms for **reference standards and test samples Select** 2. Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1)) a. Drug Substance **Select** b. API lot numbers	
	3.2.S.4.4	**Batch Analysis** 1. COAs specifications and test results from drug substance manufacturer(s) **Submitted** 2. Drug Product manufacturer's Certificates of analysis **Submitted**	
	3.2.S.4.5	**Justification of Specification Select** Provide data in tabular format: Chemical Name | Code# | MDD | IT | QT | TDI of Impurity | Proposed AC for Unspecified Impurities | Proposed AC for Specified Impurities | Justification if AC>QT for Specified Impurities http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf	
3.2.S.5		**Reference Standards or Materials** (Do NOT refer to DMF) **Select**	
3.2.S.6		**Container Closure Systems Select**	
3.2.S.7		**Stability** 1. Retest date or expiration date of API **Select**	

	3.2.P DRUG PRODUCT	COMMENT(S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) **Yes** 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) (provide justification in a tabular format) **Yes** 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) **Select** 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21 CFR 73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable) **Select** 5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration **Select**	Checked
3.2.P.2	**Pharmaceutical Development** 1. Pharmaceutical Development Report **Select** 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products b. Antimicrobial Effectiveness Testing for Multi-dose Sterile Products	
3.2.P.3	**Manufacture**	
3.2.P.3.1	**Drug Product Manufacturer(s)** Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es) of the Facility(ies) **Select** 2. Contact name, phone and fax numbers, email address **Select** 3. U.S. Agent's name (if applicable) **Select** 4. Specify function or responsibility **Select** 5. cGMP Certification from Applicant **Select** 6. CFN, FEI, or DUNS numbers (if available) **Select**	Checked
3.2.P.3.2	**Batch Formula Select**	Checked
3.2.P.3.3	**Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process and (for aseptic fill products) Facility **Select** 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified **Select** 3. Master Packaging Records for intended marketing container(s) **Select** 4. If sterile product **Select** 5. Reprocessing Statement (cite 21 CFR 211.115) from Applicant **Select**	
3.2.P.3.4	**Controls of Critical Steps and Intermediates**	
3.2.P.3.5	**Process Validation and/or Evaluation** 1. Terminally Sterilized Product **Select** • Validation of production terminal sterilization process • Validation of depyrogenation of all product containers and closures • Validation of container-closure package integrity 2. Aseptically Filled Product **Select** • Validation (bacterial retention studies) of sterilizing grade filter(s) • Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures • Validation of depyrogenation of product containers and closures • Validation of aseptic filling process/line/room (media fills/process simulations) • Validation of container-closure package integrity	
3.2.P.4	**Controls of Excipients (Inactive Ingredients)**	
*	**Source of Inactive Ingredients Identified Select**	Checked
3.2.P.4.1	**Specifications** 1. Testing specifications (including identification and characterization) **Select** 2. Supplier's COA (specifications and test results) **Select**	
3.2.P.4.2	**Analytical Procedures Select**	
3.2.P.4.3	**Validation of Analytical Procedures Select**	

	3.2.P.4.4	**Justification of Specifications** (except Applicant COA, other documents as applicable) 1. Applicant COA **Select** 2. Residual Solvents Statement(s) from manufacturer(s) **Select** 3. Bovine spongiform encephalopathy (BSE) **Select** 4. Transmissible spongiform encephalopathy (TS) **Select** 5. Melamine Certifications **Select**	

Controls of Drug Product

3.2.P.5	3.2.P.5.1	Specification(s) **Select**	Checked
	3.2.P.5.2	Analytical Procedures **Select**	
	3.2.P.5.3	Validation of Analytical Procedures (if using USP procedure, must provide verification of USP procedure) **Select** Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1)) 1. Finished Dosage Form **Select** 2. Lot numbers and strength of Drug Products	
	3.2.P.5.4	Batch Analysis Certificates of Analysis for Finished Dosage Form **Submitted Batch C-0404-31**	
	3.2.P.5.5	Characterization of Impurities **Select** Provide in tabular format as below: IUPAC Chemical Name | Code # | Chemical Structure | Degradation Impurity | Source/ Mechanism http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf	
	3.2.P.5.6	Justification of Specifications **Select**	
3.2.P.7		Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) **Select** 2. Components Specification and Test Data **Select** 3. Packaging Configurations and Sizes 4. Container/Closure Testing (recommended additional testing for all plastic) a. Solid Orals: water permeation, light transmission **Select** b. Liquids: leachables, extractables, light transmission **Select** 5. Source of supply and suppliers address **Select**	Checked

Stability

3.2.P.8	3.2.P.8.1	Stability Summary and Conclusion (Finished Dosage Form) 1. Stability Protocol Submitted **Select** 2. Expiration Dating Period for Marketed Packaging 3. Expiration Dating Period for Bulk packaging (if applicable)	
	3.2.P.8.2	Post-Approval Stability Protocol and Stability Commitment 1. Post-Approval Protocol and Commitment from Applicant **Select**	
	3.2.P.8.3	Stability Data 1. Accelerated stability data a. four (4) time points, 0,1,2,3 Yes --OR-- b. Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013 **Select** c. For liquid and semi-solid products, upright and inverted/horizontal storage orientation **Select** 2. Batch numbers on stability records the same as the test batch **Select** 3. Date accelerated stability study initiated **Select** 4. Date accelerated stability sample removed from stability chamber for each testing time point **Select**	Checked

3.2.R REGIONAL INFORMATION 21 CFR §314.50(d)(1)(ii)(b)

			COMMENT(S)
REGIONAL INFORMATION (DRUG SUBSTANCE)			
3.2.R.S Drug Substance	3.2.R.1.S	Executed Batch Records for drug substance (if available) Select	
	3.2.R.2.S	Comparability Protocols Select	
	3.2.R.3.S	Methods Validation Package (Required for Non-USP drugs) Select Methods Validation Package (3 copies for paper and N/A for E-Submissions)	

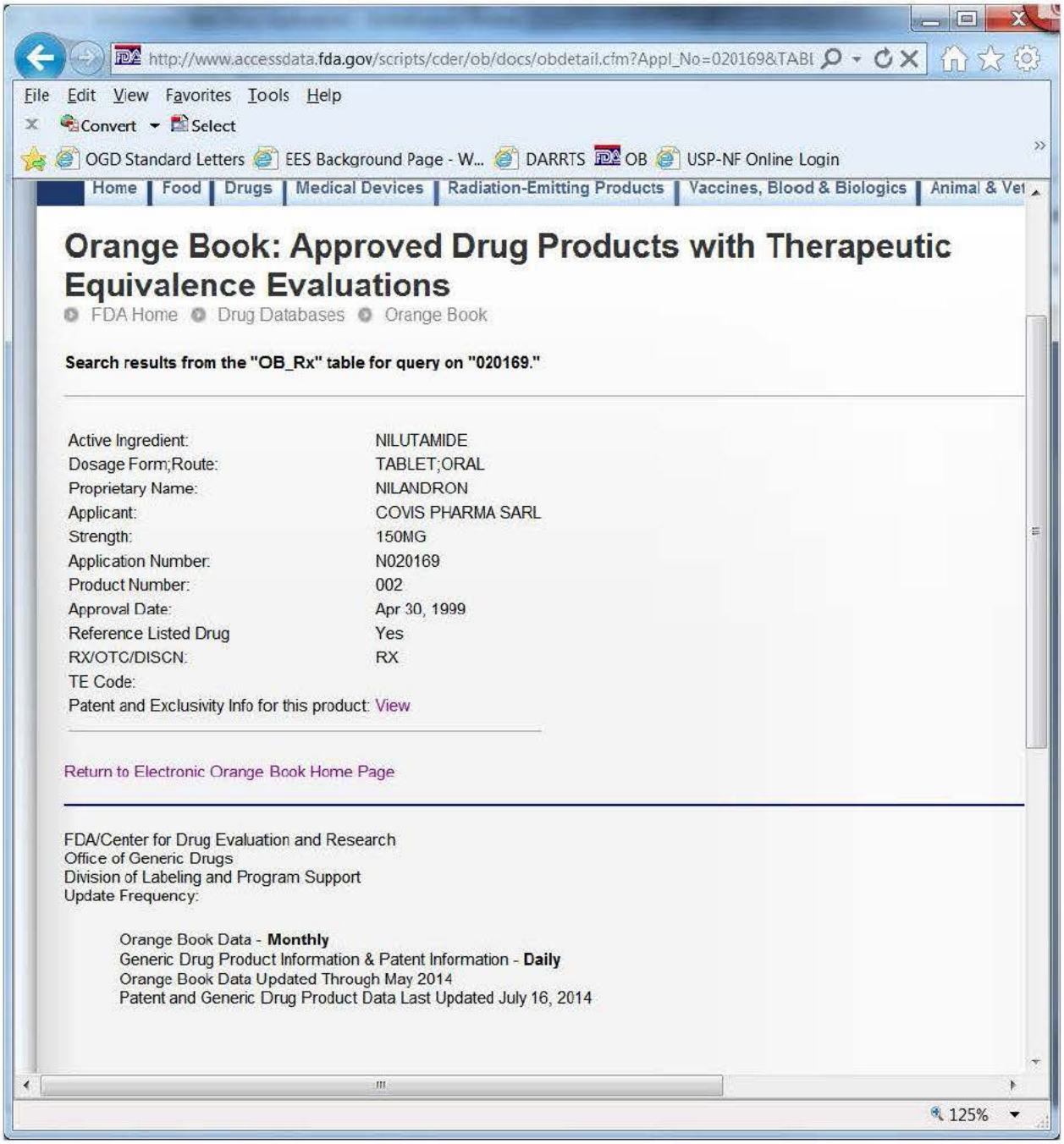
REGIONAL INFORMATION (DRUG PRODUCT)			
3.2.R.P Drug Product	3.2.R.1.P	1. Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Submitted a. Theoretical Yield b. Actual Yield c. Packaged Yield Bulk Package Reconciliation for all bulk packaging considered a commercial container is required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) Select b. Bulk Package Stability (3.2.P.8) Select 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months Select 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months Select c. Bulk Package Container and Closure information (3.2.P.7) Select 2. Information on Components Select Name(s) and Address(es) of the Active Pharmaceutical Ingredient (API), inactive ingredient(s), and containers and closures in tabular format.	Checked
	3.2.R.2.P	Comparability Protocols Select	
	3.2.R.3.P	Methods Validation Package Select Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 5: CLINICAL STUDY REPORTS

			COMMENT(S)
5.2		Tabular Listing of Clinical Studies Select	
5.3	5.3.1	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (proportionality of multiple strengths) Select b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. Lot Numbers and strength of Products used in BE Study(ies) 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	
	*	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. The study data that support the BA/BE summary tables should be provided in the corresponding sections below: 5.3.1.2 Comparative BA/BE Study Reports 5.3.1.3 In Vitro-In Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7) 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies Case Report Forms should be placed under the study to which they pertain, and appropriate tagged. Refer to The eCTD Backbone File Specification for Study Tagging http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4		Literature References	
		Possible Study Types:	
Study Type		IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, Cmax , AUC) Yes 2. In-Vitro Dissolution Yes	Checked
Study Type		IN-VIVO BE STUDY with CLINICAL ENDPOINTS Division of Clinical Review Consult Complete ☐ Yes ☐ No	
Study Type		IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. In-Vitro Dissolution Select	
Study Type		NASALLY ADMINISTERED DRUG PRODUCTS Refer to the attached links for Nasal Product BE Tables: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf AND http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type		IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type		TRANSDERMAL DELIVERY SYSTEMS Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Effective as of June 20, 2014

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
Draft Guidance for Industry ANDA Submissions – Content and Format of Abbreviated New Drug Applications:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf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Convert Select
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Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Vet
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
FDA Home Drug Databases Orange Book
Search results from the "OB_Rx" table for query on "020169."
Active Ingredient: NILUTAMIDE
Dosage Form;Route: TABLET;ORAL
Proprietary Name: NILANDRON
Applicant: COVIS PHARMA SARL
Strength: 150MG
Application Number: N020169
Product Number: 002
Approval Date: Apr 30, 1999
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May 2014
Patent and Generic Drug Product Data Last Updated July 16, 2014
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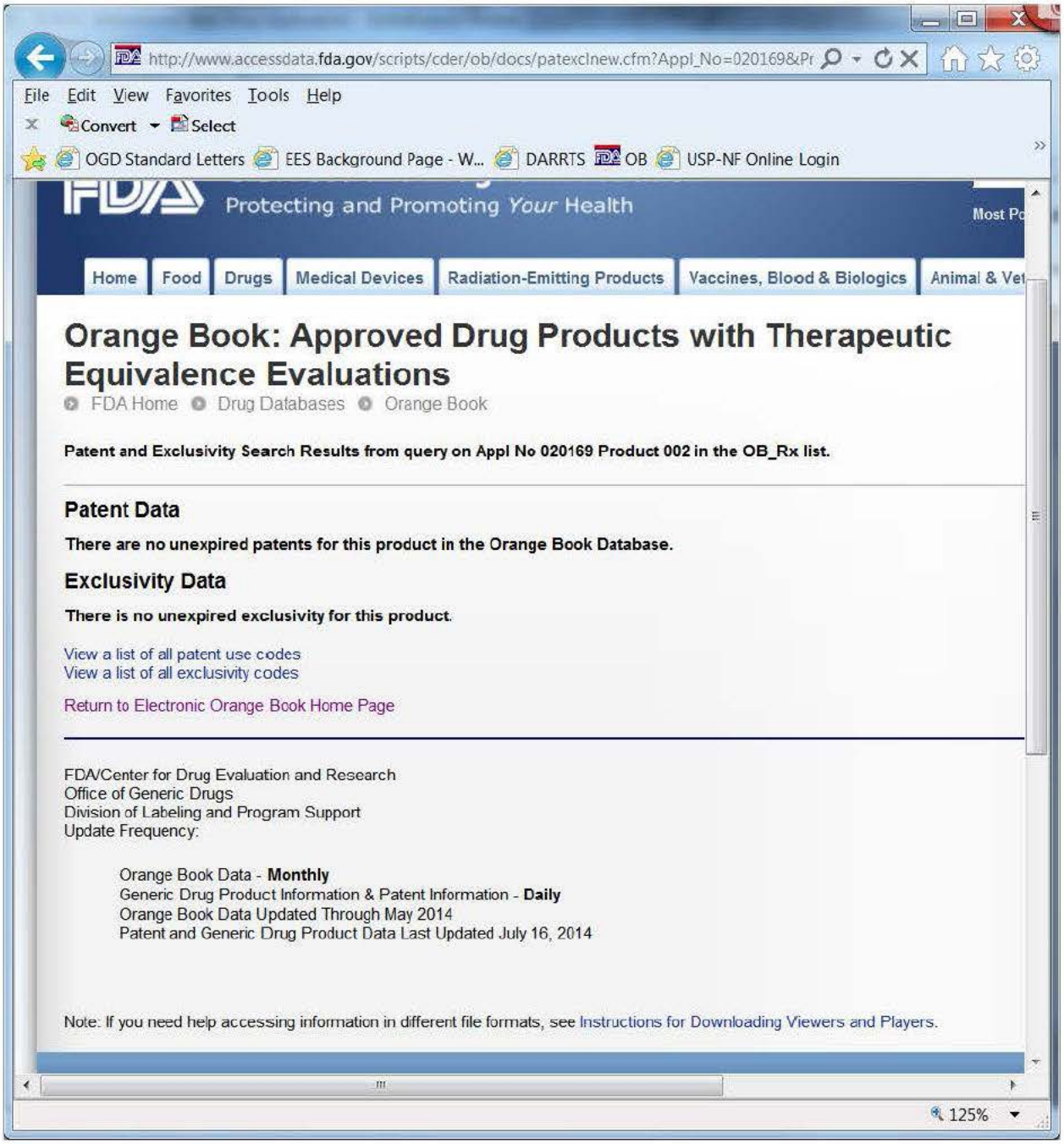
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OGD Standard Letters EES Background Page - W... DARRTS OB USP-NF Online Login
Protecting and Promoting Your Health
Most Po
Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Vet
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
FDA Home Drug Databases Orange Book
Patent and Exclusivity Search Results from query on Appl No 020169 Product 002 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
Exclusivity Data
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May 2014
Patent and Generic Drug Product Data Last Updated July 16, 2014
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
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DRUG PRODUCT FORMULATION			
PROPOSED ANDA DRUG PRODUCT	**AMOUNT/DOSE**	**%w/w**	**AMOUNT PER BATCH**
Nilutamide	150.0 mg[¥]		
[redacted]			
Lactose [redacted] NF			
Povidone, USP			
Docusate Sodium, USP			
Talc, USP			
Calcium Stearate, NF			
[redacted]			

INACTIVE INGREDIENTS	ROUTE; DOSAGE FORM	LAST NDA	APPROVAL DATE	MAXIMUM POTENCY/UNIT
[redacted]	ORAL; TABLET	N072004	11/18/1987	435.8MG
LACTOSE [redacted]	ORAL; TABLET	N077766	12/20/2006	586MG
POVIDONE [redacted]	ORAL; TABLET	N076411	6/20/2003	49.55MG
DOCUSATE SODIUM	[redacted]			
TALC	ORAL; TABLET	N071644	2/1/1988	91.2MG
CALCIUM STEARATE	[redacted]			

Guidance on Nilutamide

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Nilutamide

Form/Route: Tablet/Oral

Recommended studies: 1 study

Type of study: Steady-State
Design: Steady state, two-way crossover or parallel *in-vivo* study
Strength: 150 mg
Subjects: Patients who are already receiving the drug at a dose of 150 mg once a day as their individual therapy and continuing on the same dose for both periods of the crossover study.

Analytes to measure (in appropriate biological fluid): Nilutamide in plasma

Bioequivalence based on (90% CI): Nilutamide

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

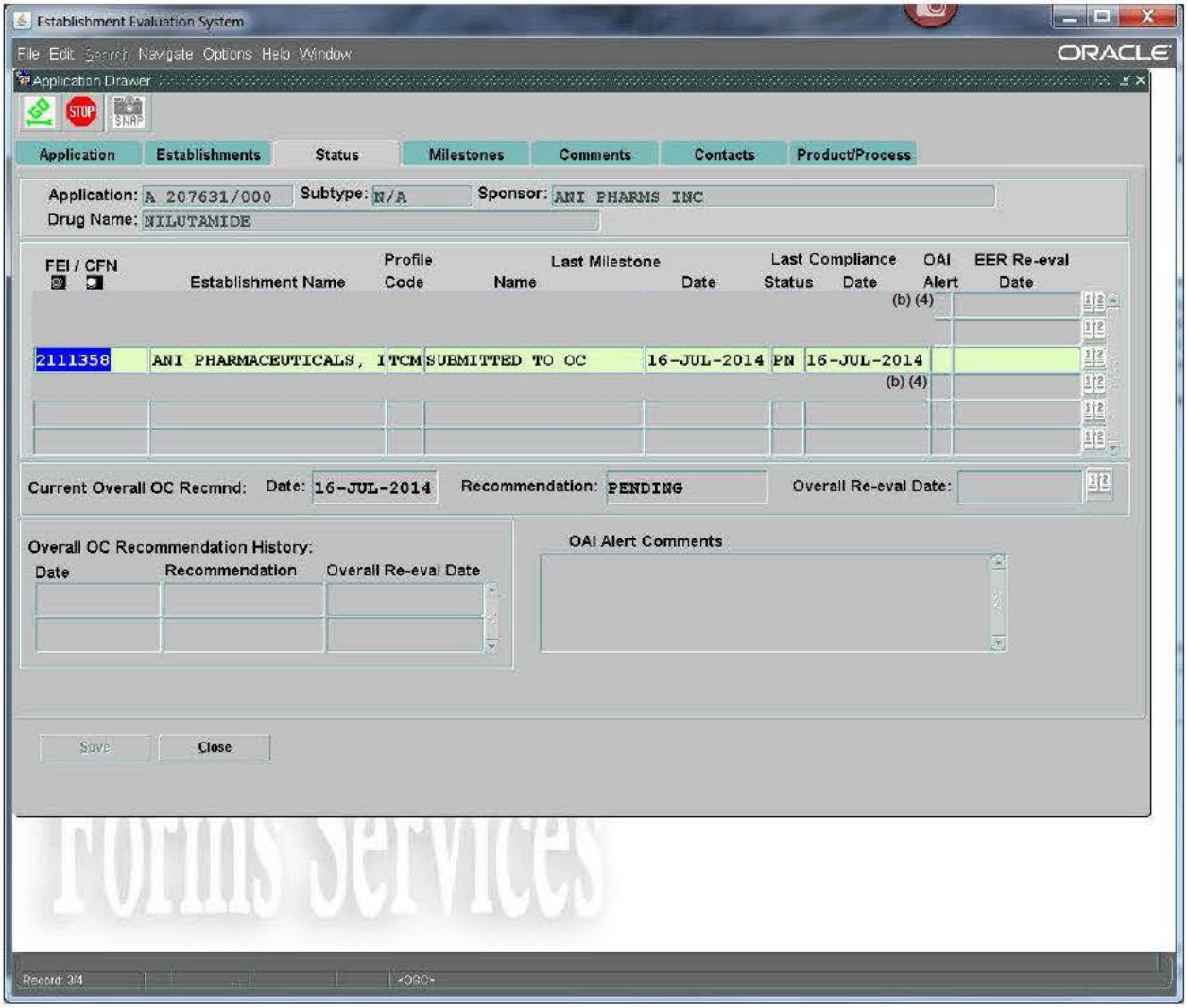
Reference Scaled Average Bioequivalence Approach Used	☐ Yes	X No

If No, then complete Table 3A only

If Yes, then complete Tables 3A and 3B

Drug (No of subjects completed= 36)
Dose (# 150 mg)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasted Bioequivalence Study (Study No. ANI-NIL.T-07.13-166/127)

Parameter	Test	N	Reference	N	Ratio	90% C.I.	
Cmaxss	A	36	B	36	99.57785	95.60172-	103.7194
Cminss	A	36	B	36	100.3596	95.73246-	105.2103
AUC0-tau	A	36	B	36	99.02353	95.84054-	102.3122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ORACLE
Application Drawer
STOP
SNAP
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 207631/000
Subtype: N/A
Sponsor: ANI PHARMS INC
Drug Name: NILUTAMIDE
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
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(b) (4)
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/s/

PETER CHEN
08/08/2014

IAIN MARGAND
08/08/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207631

ANI Pharmaceuticals, Inc.
Attention: Ellen Camos
210 Main Street West
Baudette, MN 56623

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

In accordance with your request for expedited review under 5240.3, the Office of Generic Drugs has granted expedited review to this ANDA.

NAME OF DRUG: Nilutamide Tablets, 150 mg

DATE OF APPLICATION: June 18, 2014

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 18, 2014

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Dat Doan
Regulatory Project Manager Team Leader
240-402-8926

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

IAIN MARGAND
08/08/2014
Signing for Wm Peter Rickman