CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	209449
Priority or Standard	Standard
Submit Date	9/26/2016
Received Date	9/26/2016
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Division/Office	DGIEP/ODE III/OND
Reviewer Name	Patroula Smpokou, MD
Review Completion Date	06/30/2017
Established Name	nitisinone
(Proposed) Trade Name	Nityr
Applicant	Cycle Pharmaceuticals Ltd
Formulation(s)	2, 5, 10 mg tablets for oral use
Dosing Regimen	0.5-1 mg/kg orally twice daily
Applicant Proposed Indication/Population	treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Recommendation on Regulatory Action	Approve
Recommended Indication/Population	treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Nityr (nitisinone tablets) was studied in two bioequivalence studies and one food effect study as compared to the listed drug, Orfadin capsules. Nitisinone is a competitive inhibitor of the enzyme 4-hydroxyphenyl pyruvate dioxygenase, an enzyme upstream of FAH (the enzyme involved in HT-1) in the tyrosine degradation pathway (figure 1). Nitisinone was approved as Orfadin capsules for oral use in 2002 for the treatment of Hereditary Tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. The sponsor submitted a NDA for a new dosage form of nitisinone (a thermally stable tablet) through the 505(b)(2) regulatory pathway relying on the FDA's finding of safety and efficacy for Orfadin capsules (NDA 021232), the reference listed drug. The sponsor's proposed indication is the same as for Orfadin, the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The product's efficacy was not assessed as part of this NDA. Of note, the Office of Clinical Pharmacology determined that the sponsor demonstrated bioequivalence between the proposed product nitisinone 10 mg tablet and the reference listed drug, Orfadin 10 mg capsule.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Not applicable as this is a 505(b)(2) NDA application which relies on FDA's findings of safety and efficacy for Orfadin capsules, the reference listed drug. The benefit-risk assessment for Orfadin capsules has previously been established.

2 Therapeutic Context

2.1. Analysis of Condition

Hereditary Tyrosinemia type 1 (HT-1), also known as hepatorenal tyrosinemia, is an inborn error of tyrosine (Tyr) metabolism caused by deficient activity of the enzyme fumarylacetoacetate hydrolase (FAH). With an incidence of 1:100,000-120,000 live births, it is a rare autosomal recessive disease affecting both males and females equally. All ethnic populations are equally affected.

FAH is the enzyme catalyzing the final step in the biochemical pathway of tyrosine degradation (figure 1). Deficiency of FAH leads to the accumulation of the metabolic intermediates fumarylacetoacetate and maleylacetoacetate which cause hepatic and renal damage. In turn, their derivatives succinylacetone (SA) and succinylacetoacetate (SAA) accumulate inhibiting porphobilinogen synthesis; this, in turn, leads to accumulation of delta-aminolevulinate (δ-ALA) which causes porphyria-like neurologic crises (described in further detail below).

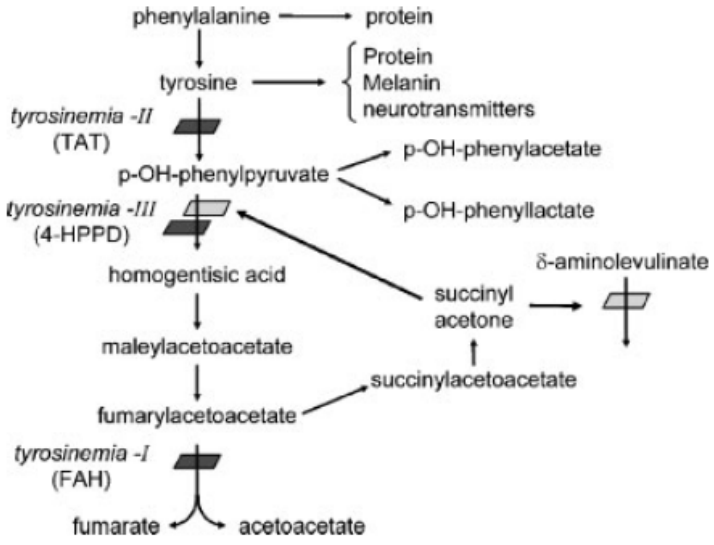

Figure 1: the tyrosine catabolic pathway[1]

The organs primarily affected in HT-1 include the liver, kidneys, and peripheral nervous system. Liver disease is the fundamental clinical manifestation in patients with HT-1 and presents in most (untreated) cases as acute liver failure in infants less than 6 months old. These patients manifest all the clinical signs and symptoms of acute liver failure including edema/ascites, coagulopathy/bleeding, and jaundice. If untreated, this can slowly progress to liver cirrhosis and the development of liver nodules and hepatocellular carcinoma. Renal tubular dysfunction, of varying severity, causing aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis (renal Fanconi syndrome) is also an important finding; this can lead to hypophosphatemic rickets and growth failure. Over time, the renal disease may progress to nephrocalcinosis, glomerulosclerosis, and chronic renal failure. The neurologic manifestations of HT-I are more rare and manifest as porphyria-like neurologic crises precipitated by an intercurrent illness, such as an infection. These are characterized by acute attacks of severe abdominal pain (resembling a "surgical" abdomen), painful paresthesias, autonomic signs (e.g. hypertension, tachycardia), and respiratory dysfunction[2].

Prior to the implementation of expanded newborn screening in the US which enables presymptomatic identification and treatment of newborns with HT-1, the clinical presentation of patients with HT-1 was divided into two broad clinical categories based on time of first onset of symptoms; in the first category, infants present before 6 months of age with severe liver disease and associated morbidities; in the second category, children present after 6 months of age with liver dysfunction of variable degrees, renal involvement, growth failure, and rickets. In untreated patients with a severe clinical presentation, HT-1 is typically fatal before 2 years of age; patients with milder disease manifestations may survive longer.[1].

Currently, newborns are typically identified as part of newborn (metabolic) screening. Newborn screening entails the collection of a small amount of venous blood placed on a dried filter paper (dried blood spot) and collected at approximatley 2-3 days of life. Cases of positive screening for tyrosinemia (high blood tyrosine) are based on the finding of elevated level of tyrosine on DBS and are referred by local state health departments to the corresponding metabolic center for further evaluation. HT-1 is then confirmed after diagnostic testing is completed which shows excess succinylacetone in body fluids, typically urine and plasma. Succinylacetone is the pathognomonic metabolite which accumulates in HT-1 and confirms the diagnosis. Molecular genetic testing is available to identify the responsible gene mutations to be used for genetic counseling, family screening, and prenatal diagnosis of other family members.

2.2. Analysis of Current Treatment Options

Current treatment options for HT-1 include dietary and pharmacologic interventions aimed at reducing toxic metabolites which accumulate due to the enzymatic block in tyrosine catabolism. Those interventions are undertaken as soon as the diagnosis is established. Restriction of exogenous (dietary) intake of tyrosine and phenylalanine (which gets converted to tyrosine) is recommended for all patients with HT-1. The only approved pharmacologic treatment for HT-1 is nitisinone. Nitisinone is a competitive inhibitor of the enzyme 4-hydroxyphenyl pyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway (see figure 1). By inhibiting the upstream enzymatic reaction, the relevant biochemical intermediates are not available for conversion to the toxic metabolites generated via the FAH block as in HT-1 thereby decreasing the production of succinylacetone and related compounds.

Nitisinone (orfadin) was approved by the FDA in 2002 for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine. The approval was based on data from one open-label, uncontrolled clinical trial of 207 patients with HT-1 (diagnosed based on the presence of succinylacetone in urine or plasma) ages 0-21.7 years at enrollment (median age 9 months). Patients were treated with orfadin for a median of 22 months. The starting dose used in the trial was 0.3-0.5 mg/kg twice daily, which in some patients was increased to 1 mg/kg twice daily based on weight, biochemical, and enzyme markers. Efficacy was assessed via rates of liver transplantation (13%), liver failure (7%), malignant hepatic neoplasms (5%), benign hepatic neoplasms (3%), and porphyria (1%). The most serious adverse reactions reported during the clinical trial of orfadin included thrombocytopenia (6 patients), leukopenia, porphyria, and ocular/visual complaints (14 patients, symptom duration 5 days - 2 years) associated with elevated tyrosine levels. No patients developed infections or bleeding in association with the episodes of leukopenia and thrombocytopenia[3].

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The current NDA submission uses the 505(b)(2) regulatory pathway relying on the FDA's finding of safety and efficacy for Orfadin 10 mg capsule, which is used as the RLD for the BA/BE trials conducted by the sponsor. Orfadin was approved in the US in 2002 as orfadin capsules and oral suspension and indicated for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine. The sponsor studied the bioequivalence of a different formulation of nitisinone 10 mg tablet (thermally stable tablet) in comparison to the orfadin 10 mg capsule (RLD) in healthy adults. Efficacy data were not collected. Limited safety data were reported as part of the 3 conducted trials.

3.2. Summary of Presubmission/Submission Regulatory Activity

Two pre-IND meetings were held between FDA and the sponsor, a type B meeting on March 4, 2014 and a type C tele-conference on June 2, 2015. During both meetings, clinical pharmacology and CMC considerations relating to a 505(b)(2) NDA application for nitisinone tablets were discussed.
The sponsor submitted an application to FDA for Orphan Drug Designation for nitisinone tablets on August 3, 2016. Orphan drug designation was not granted based on lack of evidence that the new formulation (thermally-stable nitisinone tablet) is "clinically" superior (according to 21 CFR 316.3 criteria) to the approved dosage form Orfadin capsule. Subsequently, a Pediatric Development Plan was submitted to FDA requesting a waiver of pediatric studies for nitisinone tablets as the sponsor stated that "studies are impossible or highly impractical" (as per section 505B(a)(4)(A)(i) of the Act) as HT-1 is a rare disease with a birth incidence of 1:100,00. A waiver of pediatric studies will be granted.

3.3. Foreign Regulatory Actions and Marketing History

None

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The inspection report by the Office of Study Integrity and Surveillance (OSIS) determined that the clinical data submitted for the pivotal BE trial CT-003 are acceptable for FDA review and recommended accepting the data without an on-site inspection based on the recent favorable insepction results of the bioanalytical study site. In addition, during the NDA review cycle, OSIS confirmed the identity of the listed drug as Orfadin 10 mg capsule.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) determined that the proposed new drug, NITYR (nitisinone) tablets, 2mg, 5mg and 10mg, is recommended for approval from the Drug Product and Drug Substance perspective.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

No new animal studies were submitted with this NDA. Please see pharmacology/toxicology review by Dr. Ramos dated 6/15/2017.

4.5. Clinical Pharmacology

Bioequivalnce was demontrated between nitisinone 10 mg tablet and the RLD, Orfadin 10 mg capsule, as determined by the Office of Clinical Pharmacology (OCP). Also, a high-fat and high-calorie meal did not affect the nitisinone exposure and, thus, the OCP determined that the proposed dosing instruction to administer nitisinone tablers with or without food is appropriate. As such, the OCP recommended this NDA for approval. Please see clinical pharmacology review by Dr. Steven Li for further details.

4.6. Mechanism of Action

No change from the approved Orfadin capsules.

4.6.1. Pharmacodynamics

No change from the approved Orfadin capsules.

4.6.2. Pharmacokinetics

No change from the approved Orfadin capsules.

4.7. Devices and Companion Diagnostic Issues

Not applicable

4.8. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1. List of studies and safety reports discussed in the safety summary

Source of data	Study	Type of study	Subject No.
Cycle	CT-001	3-way crossover, 3-period, bioequivalence study in healthy subjects	24*
Cycle	CT-002	2-way crossover, 2-period, food effect study in healthy subjects	20
Cycle	CT-003	3-way crossover, 3-period, bioequivalence study in healthy subjects	24*

*Only 23 subjects completed the studies, one subject was withdrawn from the study in period 1 in both studies.

Table 1: source: sponsor's NDA submission, clinical overview section

The sponsor conducted two bioequivalence studies and one food effect study in healthy adults to demonstrate that nitisinone 10 mg oral tablet (test drug) is bioequivalent to Orfadin 10 mg capsule (RLD) and to assess the food effect on the bioavailability of nitisinone 10 mg tablet (test drug).

1. CT-001 is a single dose, open label, laboratory-blind, randomized, 3-period crossover trial assessing the comparative bioavailability of 2 test drug formulations (10 mg nisitinone tablet, 10 mg high-compritol nitisinone tablet) to the reference-listed drug (RLD) orfadin 10 mg capsule. The trial included 23 healthy adults and was conducted over a total of 70 days under fasting conditions (total: 46 days on nitisinone 10 mg tablet and 24 days on orfadin 10 mg capsule). The trial included 3 treatment periods separated by a 23-day washout period between consecutive administrations of the 3 products.

2. CT-002 is a single dose, open-label, laboratory-blind, randomized, 2-period crossover, food effect study of nitisinone 10 mg tablets in 19 healthy adults over a total duration of 39 days. The study included 2 treatment periods (one under fasting and another under fed conditions) separated by a 23-day washout period between consecutive administrations of the test product.

3. CT-003 (pivotal BE study) is a single center, single-dose, open-label, laboratory-blind, randomized, 3-period crossover trial assessing the comparative bioavailability of 2 test drug formulations (10 mg nisitinone tablet, 10 mg high-compritol nitisinone tablet) to the reference-listed drug (RLD) orfadin 10 mg capsule. The trial included 23 healthy adults and was conducted over a total duration of 70 days (total 46 days on nitisinone 10mg tablet and 24 days on orfadin 10 mg capsule). The trial included 3 treatment periods separated by a 23-day washout period between consecutive administrations of the 3 products.

5.2. Review Strategy

This clinical review focuses on the limited safety data submitted as part of the 3 BA/BE trials of nitisinone conducted by the sponsor as part of this 505(b)(2) NDA application. No efficacy data were collected. Also, the conducted studies were not designed to assess the safety of nitisinone as this has previously been established.

6 Review of Relevant Individual Trials Used to Support Efficacy

Not applicable

7 Integrated Review of Effectiveness

Not applicable

8 Review of Safety

The submitted BA/BE studies were not designed to assess the safety of nitisinone as the safety profile has already been established. However, AEs reported during the 3 studies conducted by the sponsor were reviewed and summarized below. Overall, no new safety signals were idenitified based on the review of the submitted trial data and nitisinone tablet was generally well-tolerated by healthy adult subjects in the submitted trials.

8.1. Safety Review Approach

All submitted laboratory, physical examination, and vital sign data for each individual patient were reviewed from the tabular submissions for each clinical study, CT-001, CT-002, and CT-003. AEs were reviewed as submitted in tabular format for each patient in each trial.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 2. Subject exposure of Nitisinone in pharmacokinetic studies

Exposure data	CT-001 Comparative bioavailability study	CT-002 Food effect study	CT-003 Pivotal bioequivalence study
Patient No.	24	20	24
Nitisinone Cycle 10 mg tablets*	46 days	39 days	46 days
ORFADIN capsules 10 mg	24 days	--	24 days
Total Nitisinone exposure	70 days	39 days	70 days

*Nitisinone Cycle includes Nitisinone Cycle, high Compritol Nitisinone Cycle and aged Nitisinone Cycle.

Table 2: source: sponsor's NDA submission, clinical overview section

8.2.2. Relevant characteristics of the safety population:

The safety population included all patients who enrolled in each trial. The patients were all healthy adults.

8.2.3. Adequacy of the safety database:

Not applicable

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues identified.

8.3.2. Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a trial subject administered a drug product, whether or not the event was thought to have a causal relationship with the treatment. Adverse events were classified as serious if they met one or more of the following criteria:

1. results in death

2. is life-threatening (i.e., at immediate risk of death
3. requires inpatient hospitalization
4. results in persistent or significant disability
5. other medically important AEs

AEs were also graded as mild, moderate, or severe defined as follows:

1. Mild: Does not interfere with subject's usual function
2. Moderate: Interferes to some extent with subject's usual function
3. Severe: Interferes significantly with subject's usual function.

For each AE, the investigator made a causality assessment to determine if there was a reasonable possibility that the adverse event was caused by the investigational drug product.

8.3.3. Routine Clinical Tests

The safety assessments including laboratory tests and vital sign measurements appear appropriate for a healthy adult trial.

8.4. Safety Results

8.4.1. Deaths

There were no deaths.

8.4.2. Serious Adverse Events

There were no serious adverse events.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In trial CT-001, one subject treated with the RLD withdrew due to the AE of vomiting. In trial CT-002, one subject withdrew due to personal reasons and not due to AE. In trial CT-003, one subject treated with RLD withdrew due to the AE of vomiting.

8.4.4. Significant Adverse Events

No significant AEs identified.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In trials CT-001 and CT-003, there were a total of 10 TEAEs (7 in trial CT-001, 3 in trial CT-003) reported in 48 healthy adults treated with nitisinone tablets (either nitisinone 10 mg tablet or the high compritol nitisinone 10 mg tablet). Of th 10 TEAEs, 5 TEAEs (3 in trial CT-001, 2 in trial CT-003) were considered possibly related to the study drug. All were mild and transient. The

most common TEAE reported was headache (n=2).

8.4.6. Laboratory Findings

There were no clinically significant laboratory abnormalities identified after thorough review of all raw data values for each patient in the 3 trials.

8.4.7. Vital Signs

There were no clinically significant vital sign abnormalities or adverse events identified after thorough review of all raw data values for each patient in the 3 trials.

8.4.8. Electrocardiograms (ECGs)

ECG was obtained on all participants at screening and those were all normal per the sponsor's assessment.

8.4.9. QT

A thorough QT assessment was not performed.

8.4.10. Immunogenicity

Not assessed and not relevant to this drug.

8.5. Analysis of Submission-Specific Safety Issues

Not applicable

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

Not applicable

8.9. Safety in the Postmarket Setting

Not applicable.

8.10. Additional Safety Issues From Other Disciplines

not applicable

8.11. Integrated Assessment of Safety

The safety profile of nitisinone is already established and no additional safety risks were identified. Nitisinone 10 mg tablets was generally well-tolerated in healthy adults who participated in studies CT-001, CT-002, and CT-003.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committe Meeting or external consultations were not held.

10 Labeling Recommendations

10.1. Prescribing Information

The product's label will reflect the RLD's approved label (orfadin capsules). Updates to the clinical pharmacology section and Dosage and Administration sections are made by the corresponding disciplines based on the submitted PK data and crushing of the tablets for pediatric use (see relevant reviews for more details). Other minor editorial changes are also made to improve clarity. Final PI is under negotiation with the sponsor at the present time. Of note, table crushing instructions for pediatric administration are included in the label as well as "Instructions for Use" for administration with a syringe (see section 10.2)

10.2. Patient Labeling

"Instructions for Use" were developed for patient information on drug preparation and administration via a syringe (for use in pediatric patients who are unable to ingest the crushed tablet via mixing in semi-solid food, such apple sauce).

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

None.

12 Postmarketing Requirements and Commitments

PMC is currently in negotiation with the sponsor relating to submission of additional CMC stability data after approval.

13 Appendices

13.1. References

1. Scott, C.R., *The genetic tyrosinemias.* Am J Med Genet C Semin Med Genet, 2006. **142C**(2): p. 121-6.
2. al, D.L.e., *Recommendations for the management of tyrosinaemia type 1.* Orphanet J Rare Dis, 2013. **8**(8).
3. Package insert for Orfadin, revised 06/2016

13.1. Financial Disclosure

Finacial Disclosure form reviewed

Covered Clinical Study (Name and/or Number): CT-001, CT-002, CT-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

PATROULA I SMPOKOU
06/30/2017