Investigator Initiated Trial (IIT)

PROTOCOL TITLE: To examine the effect of Horizant (Gabapentin Enacarbil) in primary Restless legs syndrome (RLS) patients who are on dopaminergic agents and exhibiting augmentation.

PROTOCOL NUMBER: XP-IIT-0034

ORIGINAL DATE: 10 DECEMBER 2014
AMENDMENT 1: 9 SEPTEMBER 2015
AMENDMENT 2: 16 OCTOBER 2015
AMENDMENT 3: 3 DECEMBER 2015
AMENDMENT 4: 18 MAY 2016
AMENDMENT 5: 06 JULY 2016
AMENDMENT 6: 18 NOVEMBER 2016
AMENDMENT 7: 03 FEBRUARY 2017
AMENDMENT 8: 08 December 2017

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AFFILIATION: UNIVERSITY OF MISSOURI-COLUMBIA – SCHOOL OF MEDICINE

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2 ACRONYMS AND ABBREVIATIONS

PI = Principal Investigator
Subject = Patient = Study Participant
RLS = Restless Legs Syndrome
IRLS = International Restless Legs Syndrome-Rating Scale
ASRS = Augmentation Severity Rating Scale
RLS-QOL = Restless legs Syndrome–Quality of Life
MOS-SS = Medical Outcome Study–Sleep Scale
DA = Dopaminergic Agents
SSRIs = Selective Serotonin Reuptake Inhibitors
CBC with differential = Complete Blood Count with differential
CMP = Comprehensive Metabolic Panel
FDA = Food and Drug Administration

3 STUDY FLOW CHART

	Pre-Rx 'Screening Phase' (duration = 15 days)	Baseline	Rx Phase 1		Rx Phase 2		
		Day 0 +/-7	Day 30 +/-7	Day 90 +/-14	Day 120 +/-14	Day 180 +/-14	Day 360 +/-14
Enrolment Period	1 year						
Medical History**	X	X	X	X	X	X	X
Concomitant Medication(s)	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X
ASRS(*)	X	X	X	X	X	X	X
IRLS(*)	X	X	X	X	X	X	X
RLS-QOL(*)		X	X	X	X	X	X
MOS-SS(+*)		X	X	X	X	X	X
CBC and differential, CMP	X		X				X
Monitoring & Recording of Adverse Events		X	X	X	X	X	X
Urine pregnancy analysis	X	X	X	X	X	X	X
Urine sample collection (drug screen)	X						
Serum pregnancy analysis Serum Ferritin Level	TBD	TBD	TBD	TBD	TBD	TBD	TBD

Rx Phase 1 (Day 0-90) = Stable DA + Horizant
Rx Phase 2 (Day 120-360) = DA taper/Horizant only

+ = Subjects will also be requested to keep a sleep diary.
* = See attachments.
** = Medical history includes Interval history between clinic visits.

4. SUMMARY

Study Title: To examine the effect of Horizant (Gabapentin Enacarbil) in primary Restless legs syndrome (RLS) patients who are on dopaminergic agents and exhibiting augmentation.

Objectives:
The Primary objective: is to evaluate the efficacy of Dopamine combined therapy with addition of Horizant (600 mg, oral, once daily) for 90 days in the treatment of Augmentation.

The Secondary objectives: is to evaluate the efficacy of Horizant (600 mg, oral, once daily) alone with Dopaminergic (DA) taper for up to 270 days in the treatment of Augmentation.

Study Design:

This is an Open label single arm study. The purpose of the study is to demonstrate the efficacy of Horizant in patients with RLS who exhibit augmentation while on Dopaminergic therapy. Adult patients (age 18-85 years) with diagnosis of primary RLS (diagnosed by study investigators) with augmentation on dopaminergic therapy will be screened for participation in the study. RLS diagnosis will be made by the study investigators using International RLS study group criteria. Patients with augmentation on dopaminergic therapy as defined by NIH 2007 (refer to attachment) with ASRS of 5 to 15 will be offered to participate in the study. Inclusion and exclusion criteria are listed below. The study will be performed after approval of the Institutional Review Board of the University of Missouri.

A total of 50 subjects will be entered into the study over a period of 1 year. Written consent will be obtained from all patients. After pre-participation evaluation for eligibility, subjects will be selected and enrolled in the study and followed for a total of 6 follow up visits (Days 0, 30, 90, 120, 180, 360). Subjects Enrollment period will last up to 12 months. The total duration of study will be 24 months.

Pubmed search (using words Horizant, Augmentation) pulled out several articles (see attachments) indicating Horizant is the “only FDA approved Non-Dopaminergic Drug” used in the treatment of RLS. Its predictable bioavailability, acceptable safety profile and no case reports of augmentation after its use, in the literature makes Horizant the best-suited drug for conducting a clinical drug trial focused on examining its potential benefit in RLS patients who developed augmentation.

Abrupt withdrawal of DA agent can be potentially dangerous due to DA withdrawal symptoms including life-threatening Neuroleptic Malignant Syndrome. Therefore, Rx Phase 1 and Rx Phase are designed to help improve subject tolerability.

Therefore, during Rx Phase 1, Horizant (600 mg oral once daily at 5 pm) will be added on as an adjunct to all subjects' along with stable dose of their current dopaminergic (DA) agent and both medications will be continued for a total period of 90 days from day 0 to day 90.

At the 90th day follow-up visit, with initiation of Rx Phase 2, all subjects will be tapered off (by 50% reduction in dose each week) of their current dopaminergic agent while maintaining the same dose of Horizant and will be on Horizant monotherapy. All subjects will be followed for additional three follow up clinic visits (days 120, 180, 360).

During this period all subjects will be monitored for symptoms of dopamine withdrawal or worsening of RLS or emergence of other symptoms which will be managed clinically by physicians. All subjects will continue to be on Horizant for the entire duration of this study with close follow up. Of note, if deemed appropriate for reasons related to safety, tolerability, and continuation of the study, the PI, at his discretion, may modify the tapering schedule of the DA although every attempt will be made to adhere to the protocol specified schedule of DA tapering.

During each clinic visit all subjects will undergo careful evaluations (by a physician) that will include: medical history such as appearance of any new health problems, any new symptoms/ adverse events between clinic visits, concomitant medication(s) history (medication reconciliation), physical examination with assessment of vital signs, ASRS, IRLS, RLS-QOL, and MOS-SS.

All subjects will undergo laboratory testing (CBC with Diff and CMP) during screening, on day 30 and day 360 (final clinic visit). In addition, urine sample will be collected at screen visit for illegal drug testing. Additional hematology and urine sample analysis for illegal drug will be performed as needed at the discretion of the investigators if an adverse event is reported by a subject. Serum Ferritin level will be performed as needed at the discretion of the investigators.

Urine pregnancy screening is required for all females of childbearing potential at screen and each clinical visits, if positive, serum pregnancy test will be performed. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.

At study completion, appropriate statistical analysis will be performed to evaluate the outcomes. We plan to publish the findings and results of this study.

Study Population:
Primary RLS patients who developed augmentation on DA therapy and score of 5 to 15 on ASRS scale.
We plan to recruit 50 patients; male and female, age 18-85 years.

Recruitment site is University of Missouri-Columbia. We may use advertisement(s) in the local media to recruit subjects.

Outcome Parameters/Evaluation:
The Primary outcome parameter:

1) A reduction in the Augmentation Severity Rating Scale (ASRS)
2) Improvement in the International Restless Legs Syndrome-Rating Scale (IRLS)
3) Improvement in the Restless Legs Syndrome-Quality of Life (RLS-QOL)
4) Improvement in the Medical Outcome Study-Sleep Scale (MOS-SS)

The Secondary outcome parameters:

1) A reduction in the Augmentation Severity Rating Scale (ASRS)
2) Improvement in the International Restless Legs Syndrome-Rating Scale (IRLS)
3) Improvement in the Restless Legs Syndrome-Quality of Life (RLS-QOL)
4) Improvement in the Medical Outcome Study-Sleep Scale (MOS-SS)

Treatment Group: This is a Single Arm study. All subjects will receive Horizant 600 mg once daily.

5. BACKGROUND

5.1 Study Rationale:

RLS is common condition that is usually treated with dopaminergic medications. Augmentation is the main complication during long-term DA treatment of RLS. It was first described in 1996 with overall increase in severity of RLS symptoms typically more severe than pre-dopaminergic therapy with earlier occurrence of symptoms and involvement of previously uninvolved extremities. It can be a very devastating experience in some patients. Augmentation is reported in up to 82% of people taking levodopa (Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205-13)

Features of Augmentation include earlier onset of RLS symptoms, increased severity of symptoms, reduced time before symptoms begin when resting, spread of symptoms to previously uninvolved body parts, and reduced effectiveness of medications including longer time before medication begins to work and less ability to decrease symptoms.

Augmentation severity can be assessed by a validated scale, ASRS, in these patients.

Management of Augmentation has not been studied in clinical trials. Presently, there is no approved medication (by FDA) to treat augmentation. In addition, currently, there are no specific practice guidelines as to how to treat augmentation. 'More research is needed to identify the optimal approach for treating augmentation once it develops. Sudden withdrawal of the offending dopaminergic drug does not appear to be a well-tolerated strategy' (Kurlan. Journal of Parkinsonism & Restless Legs Syndrome Vol 3, 49-52, 2013).

Pubmed search (conducted in Jan 2015, with key words "Horizant, Augmentation") revealed several articles (see attachments) suggesting that Horizant is the only FDA approved Non-dopaminergic drug used in the treatment of RLS, with predictable bioavailability, acceptable safety profile and with any reports of augmentation. Therefore, we suggest that Horizant may be a best-suited drug to treat augmentation in RLS patients. Thus, we propose to conduct a clinical drug trial to examine Horizant in RLS patients who developed augmentation.

Abrupt withdrawal of DA agent can be potentially dangerous due to DA withdrawal symptoms including life-threatening Neuroleptic Malignant Syndrome. Therefore, to improve subject tolerability and minimize DA withdrawal, we have designed this clinical trial into 2 phases: Rx Phase 1 and Rx Phase 2 (described below)

6. Objectives:

The Primary objective: is to evaluate the efficacy of Dopamine combined therapy with addition of Horizant (600mg, oral, once daily) for 90 days in the treatment of Augmentation.

The Secondary objectives: is to evaluate the efficacy of Horizant (600 mg, oral, once daily) alone with Dopaminergic (DA) taper for up to 270 days in the treatment of Augmentation.

6.1 Study Design:

This is an Open label Single arm study. The purpose of the study is to demonstrate the efficacy of Horizant in patients with RLS who exhibit augmentation while on Dopaminergic therapy. Adult patients (age 18-85 years) with diagnosis of primary RLS (diagnosed by study investigators) with augmentation on dopaminergic therapy will be screened for participation in the study. RLS diagnosis will be made by the study investigators using International RLS study group criteria. Patients with augmentation on dopaminergic therapy as defined by NIH 2007 (refer to attachment) with ASRS of 5 to 15 will be offered to participate in the study. Inclusion and exclusion criteria are listed below. The study will be performed after approval of the Institutional Review Board of the University of Missouri.

A total of 50 subjects will be entered into the study over a period of 1 year. Written consent will be obtained from all patients. After pre-participation evaluation for eligibility, subjects will be selected and enrolled in the study and followed for a total of 6 follow up visits (Days 0, 30, 90, 120, 180, 360). Subjects Enrollment period will last up to 12 months. The total duration of study is 36 months.

There is no report of Augmentation due to Horizant use in the literature to this date. Therefore, initially Horizant (600 mg oral once daily at 5 pm) will be added on as an adjunct to all subjects' along with stable dose of their current dopaminergic (DA) agent and both medications will be continued for a total period of 90 days from day 0 to day 90.

At the 90th day follow-up visit, while maintaining the same dose of Horizant, all subjects will be tapered off (by 50% reduction in dose each week) of their current dopaminergic agent. Subsequently all subjects will be followed for additional three follow up clinic visits (days 120, 180, 360). During this period all subjects will be monitored for symptoms of dopamine withdrawal or worsening of RLS or emergence of other symptoms which will be

managed clinically by physicians. If deemed appropriate for reasons related to safety, tolerability, and continuation of the study, the PI at his discretion may modify the tapering schedule of the DA although every attempt will be made to adhere to the protocol specified schedule of DA tapering. All subjects will continue to be on Horizant for the entire duration of this study with close follow up.

During each clinic visit all subjects will undergo careful evaluations (by a physician) that will include: medical history such as appearance of any new health problems, any new symptoms/ adverse events between clinic visits, concomitant medication(s) history(medication reconciliation), physical examination with assessment of vital signs, ASRS, IRLS, RLS-QOL, and MOS-SS.

All subjects will undergo laboratory testing (CBC with Diff and CMP) during screening, on day 30 and day 360 (final clinic visit). In addition, urine sample will be collected at screen visit for illegal drug testing. Additional hematology and urine sample analysis for illegal drug will be performed as needed at the discretion of the investigators if an adverse event is reported by a subject. Serum Ferritin level will be performed as needed at the discretion of the investigators.

Urine pregnancy screening is required for all females of childbearing potential at screen and each clinical visits, if positive, serum pregnancy test will be performed. Female subjects who have undergone surgical sterilization, who are post-menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.

Study Procedure
If you agree to be in this study, you will sign this form before any study tests are done.
Talk with your study doctor before starting any new medicine. This includes medicines you buy at the drug store and herbal or dietary supplements (vitamins). Some drugs, as well as alcohol, use can cause serious side effects if taken with the study drug.
Please ask your study doctor if you have any questions about the medicine(s) you are taking. He/she will tell you which medicine you cannot take during the study.
This study has four periods: screening, treatment and maintenance and follow-up.

Visit 1: Screening Period, (prior to treatment with study drug)

Before you begin taking study drug, subject will need to have the following tests to find out if you can be in the study.
- Medical history: We will ask about your health and any illnesses and any medicines you are taking or have taken within the last 30 days (including over-the-counter medicine, vitamins or herbal supplements and how much caffeine you use weekly).
- We will ask you about your current and prior Augmentation treatment, symptoms, your usual bedtime and awakening times.

- You and the staff will complete assessments on how you are feeling and if you have any thoughts about harming yourself.
- Physical examination: You will have a full physical examination including neurological exam, height and weight.
- Vital signs: You will have your temperature, heart rate, blood pressure, temperature and breathing rate collected.
- Urine testing: You will collect a sample of urine for illegal drug screening and pregnancy testing.
- Blood testing: We will collect blood samples (2 teaspoons or~10ml) for lab tests including hematology. Additional blood sample (~1/4 of teaspoon or 1.25ml) will be collected if you are a woman and your urine pregnancy test turn positive.
- Augmentation severity rating scale (ASRS) – 3 item questionnaire to evaluate the severity of your augmentation symptom.
- International restless legs syndrome-rating scale (IRLS) - a way to measure severity of your symptoms.
- If you are a woman and can have children you must use a medically acceptable method of contraception which can include estrogen-progestin oral contraceptive pills, patches, or vaginal ring (if one of these methods is chosen it must have been used consistently for 2 months prior to the first dose of study drug); progestin implant or injection; diaphragm with spermicide; male condom plus vaginal spermicide; surgical sterilization; intrauterine device; vasectomy of the partner or spouse (>6 months prior to baseline).
- If you are a man, you should not father children while in the study. Your study doctor will talk to you about either agreeing to use specific methods of birth control or agreeing to abstain from sexual intercourse during the study and for 30 days after study completion.
- We will instruct you on how to discontinue any medications not allowed while you are in the study. Without your regular medications, your medical conditions or symptoms may get worse however, we will check with the doctor that prescribed the medication to make sure that it is safe for you to stop taking it. You might not be able to drive or operate machinery. If your medical conditions or symptoms do get worse, please call the study doctor at the phone number provided in this consent form.
- We will make an appointment for you to return for Visit 2 (baseline visit), within the next 15 days or less.

Visit 2 (day 0+/-7), visit 3 (day 30+/-7), visit 4 (day 90+/-14), visit 5 (day 120+/-14), visit 6 (day 180+/-14) and visit 7 (day 360+/-14) will have the following tests and procedures except that visit 2, 4, 5 and 6 will not have blood sample collection.

- Medical history: We will ask about your health and any illnesses and any changes in medicines you are taking or have taken since last visit.
- We will ask you about your current and prior Augmentation treatment, symptoms, your usual bedtime and awakening times.
- You and the staff will complete assessments on how you are feeling and if you have any thoughts about harming yourself.
- Physical examination: You will have a full physical examination including neurological exam, height and weight.

- Vital signs: You will have your temperature, heart rate, blood pressure, temperature and breathing rate collected.
- Blood testing: We will collect blood samples (2 teaspoon or~10ml) for lab tests including hematology. Additional blood sample (~1/4 of teaspoon or 1.25ml) will be collected if you are a woman and your urine pregnancy test turn positive.
- Urine testing: You will collect a sample of urine for pregnancy testing.
- Augmentation severity rating scale (ASRS) – 3 item questionnaire to evaluate the severity of your augmentation symptom.
- International restless legs syndrome-rating scale (IRLS) - a way to measure severity of your symptoms.
- Restless legs syndrome-quality of life (RLS-QOL) – a way to measure improvement in quality of your life.
- Medical outcome study-sleep scale (MOS-SS) - a way to assess your sleep.

Blood sample collection: a blood sample (2 teaspoon or ~10ml) will be collected for complete blood count with differential and comprehensive metabolic panel at screening visit, visit 3 (day 30) and visit 7 (Day 360). In addition, it will be performed as needed at the discretion of the investigators if an adverse events is reported by a subjects. In other words, if a side effect occurs and the investigator feels additional tests will be helpful, then it will be done. Additional blood sample (~1/4 of teaspoon or 1.25ml) will also be collected if urine pregnancy test turn positive. Serum Ferritin level will be performed as needed at the discretion of the investigators. The total amount of blood sample collected will be 6-7 teaspoon or 30-35ml for the entire study.

7. STUDY POPULATION:

7.1 Number of Subjects: 50 (we believe that we will be able to recruit only 50 eligible subjects during the one year enrollment period)

7.2 Inclusion Criteria:

To be eligible for entry into this study, candidates must meet **all** of the following eligibility criteria before enrollment:

1. Adult patients with diagnosis of RLS for more than one year.
2. Patients who are on DA therapy for 6 months or longer.
3. Patients who developed Augmentation (on stable dose of DA) lasting for 3 months or longer.
4. Augmentation severity rating scale of 5 to 15.
5. Both males and females
6. Age range = 18-85 year

7.3 Exclusion Criteria:

Candidates will be excluded from study entry if **any** of the following exclusion criteria exist at the time of screening phase.
Patients who have history of:

- Known Hypersensitivity to Horizant or Gabapentin products
- Peripheral neuropathy
- Radiculopathy
- Peripheral vascular disease
- Uremia (abnormal BUN or Creatinine on CMP)
- Anemia
- Patients who are currently pregnant
- Patients who currently take opioids, lithium, anti-nausea medications (e.g. metoclopramide), dopaminergic antagonists (e.g. Haloperidol), 1st generation antihistamines (e.g. diphenhydramine, pseudoephedrine), anti-psychotic medications and iron therapy.
- Subjects with impaired decision making capability.

7.4 Medical History Exclusions: as per Exclusion criteria

7.5 Treatment History Inclusions or Exclusions: as per Inclusion and Exclusion criteria

7.6 Miscellaneous : Not applicable

7.7 Screening Log: will be maintained

Participating center is required to document all screened candidates initially considered for inclusion in this study and to specifically state the reason(s) for their exclusion.

8. STUDY MEDICATION, DESCRIPTION, AND ALLOCATION

Study drug is not to be used beyond the initial expiration date on the drug packaging.

8.1 Horizant Stability & Storage

HORIZANT Extended-Release Tablets containing 600 mg of gabapentin enacarbil are white to off-white, with occasional black/grey spots, oval-shaped tablets debossed with "GS LFG". They are supplied as follows:
600 mg: NDC 53451-0101-1: Bottles of 30
Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room

8.2 Other Study Drug Generic Name (Brand Name®) – Not applicable
8.3 Randomization Procedure: Not Applicable.
8.4 Blinding Procedures – Not Applicable
8.5 Drug Accountability:
The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom they are dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed. If drug is provided by XenoPort, the investigator must return all unused vials of study drug to XenoPort Inc. pursuant to instructions (unless agreed otherwise by XenoPort Inc.).

8.6 Treatment Schedule: as per study design.

8.7 Modification of Treatment Schedule for Horizant:

If deemed necessary for individual subject's safety, it is at the discretion of the treating physician to modify the schedule of dosage of 600 mg according to the approved package insert; however, every attempt should be made to maintain the scheduled study dosing.

8.8 **Modification of Treatment Schedule for Other Study Drug :** as per protocol.

8.9 Discontinuation of Subjects from Investigational Treatment or from the Study

Subjects must be withdrawn from the study for the following reasons:

1. If a subject develops significant adverse effect(s) after addition of Horizant or subject experiences significant DA withdrawal side effects as judge by the investigator.
2. If a subject is diagnosed to have a new medical condition while participating in the study that would fall into exclusion criteria (6.3) or if management of a newly diagnosed acute medical problem requires termination of the study medication.
3. If a subject becomes pregnant.
4. If a subject is deceased.
5. XenoPort Inc. may terminate this study, after consultation with investigators, at any time.

8.10 Discontinuation of Study Drug:

The reasons for discontinuation of the study drug must be recorded in the subject's case report form (CRF).

8.11 Treatment Compliance

Compliance with study drug will be monitored and recorded by study personnel based on information from the treating principal investigator and subjects.

8.12 Concomitant Therapy

All subjects will be continued on all their current medications for their medical conditions {except medications listed in item 6.3 that can potentially affect the course and/or management of RLS}.

8.13 Recording Concomitant Medication: Medication reconcilliation will be performed by study support staff/personnel and confirmed by investigator during each clinic visit

8.14 Extension Study: Not Applicable

9. SCHEDULE OF EVENTS

9.1 **Laboratory Tests:** All subjects will undergo laboratory tests (CBC with Diff and CMP) during screening phase, on day 30 and day 360 (final clinic visit). In addition, urine sample will be collected at screen visit for illegal drug screen. Additional urine illegal drug screen and hematology analysis will be performed as needed at the discretion of the investigators if an adverse event is reported by a subject. Serum Ferritin level will be performed as needed at the discretion of the investigators.

Urine pregnancy screening is required for all females of childbearing potential at screen and each clinical visits, if positive, serum pregnancy test will be performed. Female subjects who have undergone surgical sterilization, who are post- menopausal (defined as age >50 and >1 year of amenorrhea), who have medically documented ovarian failure (defined as age <50 with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine βHCG) do not need to undergo pregnancy screening.

9.2 Study Site Personnel and Responsibilities:

Where specified, evaluations described in this section must be performed only by the personnel indicated.

9.2.1 **The Independent Assessment Panel or Centralized Reading/Evaluating Group:** not applicable

9.3 Visits and Assessments

During each clinic visit all subjects will undergo careful evaluations (by a physician) that will include: medical history such as appearance of any new health problems, any new symptoms/adverse events, introduction of new medication(s) between clinic visits, concomitant medication(s){medication reconciliation}, physical examination with assessment of vital signs, ASRS, IRLS, RLS-QOL, and MOS-SS.

10. EFFICACY ASSESSMENTS

10.1 Clinical Efficacy Assessments include documenting ASRS, IRLS, RLS-QOL and MOS-SS each visit.

10.2 Safety and Tilerability Assessments

The safety and tolerability of Horizant will be determined by the occurrence of and/or Changes in:

- Treatment-emergent adverse events
- Any clinically significant changes in laboratory tests

• Any new complaints or significant changes in physical examination

Patients will be enquired about adverse effects during each visit.

Labs will be performed as per study design and as needed by investigator's discretion during the study

11 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS – DEFINITION & REPORTING

At the signing of the informed consent form, each subject will be given the names and telephone numbers of investigational site personnel for reporting adverse events and medical emergencies.

11.1 Definitions

11.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event is any adverse event that is experienced by a subject who has received an investigational drug, but that does not necessarily have a causal relationship with the investigational drug.

11.1.2 Serious Adverse Events

In accordance with 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonization (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45], any of the following adverse events are to be classified as a serious adverse event (SAE):

- An event that results in death.
- An event that, in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event). This does not include an event that, had it occurred in a more severe form, might have caused death.
- An outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study.
- An event that requires or prolongs in-patient hospitalization.
- An event that results in persistent or significant disability/incapacity.
- Other medically important events that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an in-patient hospitalization.).

If a serious adverse event is unresolved when a subject permanently discontinues the study, the subject will be followed until the event resolves or the clinical course is stabilized.

11.1.3 Adverse Event Recording/Reporting

All adverse events (including pre-dosing and treatment-emergent) should be recorded in the subject's record (or, if applicable, in the adverse event section of the CRF) regardless of severity or relationship to investigational drug.

11.1.4 Immediate Reporting of Serious Adverse Events

Any SAE required to be reported according to 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonization (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45] that occurs regardless of whether or not the subject has undergone any study-related procedures or received investigational drug, through the completion of trial, will be reported to the FDA. The investigator will forward a copy of the report to XenoPort in the same time frame that it is submitted to the FDA.

The Investigator will notify the local IRB/IEC per local requirements.

11.1.5 Safety Classifications

The following classifications should be considered when evaluating the relationship of adverse events and serious adverse events to investigational drug:

Relationship of Event to Investigational Drug	
Not related:	Any event that does not follow a reasonable temporal sequence from administration of investigational drug AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely:	Any event that does not follow a reasonable temporal sequence from administration of investigational drug OR that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Likely:	Any reaction that follows a reasonable temporal sequence from administration of investigational drug OR that follows a known response pattern to the suspected drug AND that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Relationship of Event to Investigational Drug	
Definitely:	Any reaction that follows a reasonable temporal sequence from administration of investigational drug AND that follows a known response pattern to the suspected drug AND that recurs with re-challenge, AND/OR is improved by stopping the drug or reducing the dose.

Severity of Adverse Events and Serious Adverse Events

The following classifications should be considered when evaluating the severity of adverse events and serious adverse events:

Severity of Event	
Mild:	Symptoms(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms(s) but may be given because of personality of subject.
Moderate:	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe:	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with investigational drug; treatment for symptom(s) may be given and/or subject hospitalized.

11.2Investigator Responsibilities

The Investigator will:

- Monitor and record all adverse events
- Determine the seriousness, causality, and severity of each adverse event
- Report all serious adverse events to the FDA according to the code of federal regulations
- Forward a copy of all serious adverse events reports sent to the FDA and XenoPort Inc. in the same time frame
- Actively and persistently pursue follow-up of serious adverse events
- Forward a copy of the follow-up information to XenoPort Inc.

11.3Additional Procedures

11.3.1 Procedures for Handling Pregnancy

Further treatment with Horizant (Gabapentin enacarbil) should be discontinued in subjects who become pregnant during the course of the study.

11.4Subject Information and Consent

Prior to any testing under this protocol, including screening tests and evaluations, all subjects will sign an informed consent form that complies with the requirements of both 21 CFR Part 50 and HIPAA before entering the study. Or, a consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA compliant authorization form for the use of and disclosure of the subject's protected health information (PHI) will be obtained from the subject in accordance with local practice and regulations.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening tests and evaluations.

11.5Subject Data Protection

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

12 ETHICAL REQUIREMENTS

The sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study according to local regulations.

12.1 Declaration of Helsinki

The Investigator must follow the recommendations contained in the Declaration of Helsinki, amended at the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. See Appendix II in Section 15.2.

12.2 Ethics Committee

The Investigator must obtain written EC/REB approval of the protocol, ICF, and other required study documents prior to starting the study. In addition, XenoPort must approve the investigational site's ICF submitted to the site's EC/REB.

13 ADMINISTRATIVE PROCEDURES

13.1 Investigational Site Initiation Visit

An investigational site initiation visit will be conducted by a representative from the sponsor prior to enrollment of any study subjects. The study site will be considered active for enrollment following a satisfactory initiation visit.

13.2 Investigator File

The Investigator should maintain an Investigator File. This file should be used for filing all study-related documents. The Investigator will be responsible for keeping the Investigator File updated and ensuring that all required documents are filed during and after the study. The Investigator File may be inspected during monitoring visits and will remain with the Investigator after the study.

13.3 Monitoring of the Study

During the course of the study, the XenoPort-designated Monitor will visit the Investigator(s) at regular intervals by prior arrangement. The monitoring visits will be conducted to ensure protocol adherence, appropriate subject enrollment, quality of data, and continued adequacy of the investigational site and its facilities.

13.4 Quality Assurance

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

13.5Study Funding

XenoPort will financially support the work of the Investigator as it pertains to the conduct of this study. All financial details are provided in a separate contract between the Investigator and XenoPort.

14 FURTHER REQUIREMENTS AND GENERAL INFORMATION

14.1External Service Organizations –Not applicable

14.1.1 Data Coordinating Center –Not applicable

14.1.2 Central Laboratories for Laboratory Evaluations–Not applicable

14.2Study Committees–Not applicable

14.2.1 Independent Assessment Panel–Not applicable

14.2.2 Publication Policy

XenoPort Inc. reserves the right to a 30-day courtesy review of all publication materials, such as abstracts, posters, or manuscripts, related to the study prior to submission of such publication(s). Investigators should refer to their Clinical Trial Agreement for additional details regarding the disclosure of study results.

14.3Changes to Final Study Protocol

All protocol amendments must be submitted to the IRB/EC. Protocol modifications that impact subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRB/EC and submitted to the appropriate regulatory authorities (if applicable) before implementation of such modifications to the conduct of the study. In the event of a protocol modification, the subject consent form also may require modifications.

It is the responsibility of the PI to submit all revisions to the protocol and consent form to XenoPort before submitting to their IRB.

14.4Record Retention

Appropriate, local, and/or institution-specific guidelines regarding retention of records must be followed.

14.5Reporting and Communication of Results

All reporting and communication of study results should be consistent with accepted publications, such as abstracts, posters, or manuscripts.

14.6Protocol Completion

The IRB/EC must be notified of completion or termination of the protocol. Within 3 months of protocol completion or termination, the investigator must provide a final clinical summary report to the IRB/EC. The principal investigator must maintain an accurate and complete record of all submissions made to the IRB/EC, including a list of all reports and documents submitted. Health Authorities of participating countries may be notified about the study end

and/or study results within defined corresponding timelines. A copy of these reports should be sent to XenoPort Inc. Adverse events, which are reported to regulatory authorities, must be submitted promptly to the IRB/EC.

14.7 STUDY TITLE: Use of and Study of Horizant in patients with Restless Leg Syndrome (RLS) on dopaminergic agonist/s exhibiting augmentation

PRINCIPAL INVESTIGATOR: Name: Pradeep Sahota MD

Institution/Organization: Neurology; University of Missouri – School of Medicine

15 REFERENCES

15.1Appendix I: Signed Agreement of the Study Protocol

I have read the foregoing protocol entitled **'**Use of Horizant in primary Restless legs syndrome (RLS) patients on dopamine agonist exhibiting augmentation' and agree to conduct the study as detailed herein and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

To be signed upon final approval

Principal Investigator's Signature Date

Pradeep Sahota, MD

Principal Investigator's Name (Print)

Neurology Dept., University of Missouri (Columbia)–School of Medicine

Investigational Site (Print)

University of Missouri – Columbia – School of Medicine

XenoPort personnel's Name and Title (Print)

XenoPort personnel's Signature

15.2 Appendix II: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for

themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

15.3

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*
2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: _____ *(mo/day/yr)*
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Disability
   ☐ Congenital Anomaly
   ☐ Required Intervention to Prevent Permanent Impairment/Damage
   ☐ Other: _____
3. Date of Event *(mo/day/year)*
4. Date of This Report *(mo/day/year)*
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
   #1
   #2
2. Dose, Frequency & Route Used
   #1
   #2
3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
   #1
   #2
4. Diagnosis for Use *(Indication)*
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # *(if known)*
   #1
   #2
7. Exp. Date *(if known)*
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# *(For product problems only)*
   – –
10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date *(mo/day/yr)* / Serial # / Other #
5. Operator of Device
   ☐ Health Professional
   ☐ Lay User/Patient
   ☐ Other:
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
   ☐ Manufacturer
   ☐ User Facility
   ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Medication errors

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures

Report SERIOUS adverse events. An event is serious when the patient outcome is:

-Fold Here-

- Death
- Life-threatening *(real risk of dying)*
- Hospitalization *(initial or prolonged)*
- Disability *(significant, persistent or permanent)*
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section C for all products except medical devices
- Attach additional blank pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

-Fold Here-

Important numbers:

- 1-800-FDA-0178 -- To FAX report
- 1-800-FDA-1088 -- To report by phone or for more information
- 1-800-822-7967 -- For a VAERS form for vaccines

To Report via the Internet:

http://www.fda.gov/medwatch/report.htm

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (12/03) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

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Penalty for Private Use $300

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MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

References/Attachments: Please refer to attached pdf files.