DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 078969

LABELING ORDER

INC Research LLC
U.S. Agent for Natco Pharma Limited
7361 Calhoun Place, Suite 500
Rockville, MD 20855

Attention: Greg Hockel
Sr. Vice President, Regulatory Consulting

Dear Dr. Hockel:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Granisetron Hydrochloride Tablets USP, 1 mg (base).

On July 10, 2014, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of granisetron hydrochloride tablets to address postmarketing reports in the FDA Adverse Event Reporting System (FAERS) and biomedical literature regarding the risk of serotonin syndrome with the use of 5-HT_3 receptor antagonists. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On August 19, 2014, we sent you an email that included revised labeling language from the original notification letter.

On September 3, 2014 and September 9, 2014, we sent follow-up emails to inquire about your intent to submit a labeling supplement as required. We also advised you that requirements under section 505(o)(4) of the FDCA apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of the application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the FDCA.

You failed to respond to our July 10, 2014, letter within 30 days and have therefore forfeited the discussion period. Under the authority of Section 505(o)(4)(E), we are ordering you to make all of the changes in the labeling listed in the July 10, 2014, letter and August 19, 2014 email (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the July 10, 2014 and August 19, 2014 email must be received by FDA by October 3, 2014, for Granisetron Hydrochloride Tablets, USP.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by September 23, 2014, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your ANDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Kyle Snyder
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3660
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Amy Bertha, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. Appeals received by the Agency later than September 23, 2014, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject

you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, contact Heidi Lee, Regulatory Project Manager, at (240) 402-8989 or heidi.lee@fda.hhs.gov.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S):
Safety Labeling Change Notification Letter
Revised Language for 5-HT_3 Receptor Antagonists Email

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 078969

SAFETY LABELING CHANGE NOTIFICATION

INC Research LLC
US Agent for: Natco Pharma Limited
7361 Calhoun Place, Suite 500
Rockville, MD 20855

Attention: Hari Nagaradona
Director, Regulatory Affairs

Dear Hari Nagaradona:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Granisetron Hydrochloride Tablets USP, 1 mg (base).

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since Granisetron Hydrochloride Tablets, USP was first approved on June 22, 2009, we have become aware of reports of serotonin syndrome related to the widespread use of the 5-HT_3 receptor antagonist class of drugs during chemotherapy and postsurgical settings as reported in the FDA Adverse Events Reporting System (FAERS) database and medical literature. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for the 5-HT_3 receptor antagonist class, and specifically for granisetron products, as follows:

HIGHLIGHTS
WARNINGS AND PRECAUTIONS
(Please add the following)

- Serotonin syndrome has been reported with granisetron, alone but particularly with concomitant use of serotonergic drugs. (5.4)

FULL PRESCRIBING INFORMATION: CONTENTS

5. WARNINGS AND PRECAUTIONS

(Please add the following)

5.4 Serotonin Syndrome

FULL PRESCRIBING INFORMATION

5. WARNINGS AND PRECAUTIONS

(Please add the following)

5.4 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagoinist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of granisetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue granisetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if granisetron is used concomitantly with other serotonergic drugs *[see Drug Interactions (7), Patient Counseling Information (17.4)]*.

7 DRUG INTERACTIONS

(Please add the following as the LAST paragraph)

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.4)]*.

17 PATIENT COUNSELING INFORMATION

(Please add the following paragraph AFTER 17.3 Exposure to Sunlight)

17.4 Serotonin Syndrome

- Inform patients that serotonin syndrome may occur, especially with concomitant use of granisetron and another serotonergic agent. Instruct patients to stop taking granisetron and seek immediate medical attention if the following symptoms occur: changes in

mental status (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea).

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you have any questions, contact Heidi Lee, Regulatory Project Manager, at (240) 276- 8989 or Heidi.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Reference ID: 3629855

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

/s/

KATHLEEN UHL
07/10/2014