DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 088704

LABELING ORDER

ClinSmart LLC
U.S. Agent for STI Pharma LLC
Attention: Donald Cox
Suite 201
2080 Cabot Boulevard West
Langhorne, PA 19047

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Triacin-C® Cough Syrup (Codeine Phosphate 10 mg/5 mL, Triprolidine HCl 1.25 mg/5 mL and Pseudoephedrine HCl 30 mg/5 mL).

On February 19, 2013, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related changes to the labeling of Triacin-C® Cough Syrup to address the risk of children developing serious adverse effects or dying after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea. 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 prior approval 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.

The 30 days have passed and we have not received any submission from you addressing our letter dated February 19, 2013.

You failed to respond to our February 19, 2013 letter within 30 days. 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 February 19, 2013 letter (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 February 19, 2013 letter must be received by FDA by May 24, 2013, for Triacin-C® Cough Syrup.

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 May 14, 2013, 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." The appeal should be submitted as 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:

Carrie Lemley
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855

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 May 14, 2013, 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, call Carrie Lemley, Labeling Project Manager, at (240) 276-8986.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Acting Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 088704

SAFETY LABELING CHANGE NOTIFICATION

ClinSmart LLC
U.S. Agent for STI Pharma LLC
Attention: Donald Cox
Suite 201
2080 Cabot Boulevard West
Langhorne, PA 19047

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Triacin-C® Cough Syrup (Codeine Phosphate 10 mg/5 mL, Triprolidine HCl 1.25 mg/5 mL and Pseudoephedrine HCl 30 mg/5 mL).

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 Triacin-C® Cough Syrup was approved on March 22, 1985, we have become aware of reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature[1,2]. These children (ages two to five) had evidence of a genetic polymorphism of cytochrome P450 2D6 (CYP2D6), resulting in their ability to convert codeine into life-threatening or fatal amounts of morphine in the body. All children had received doses of codeine that were within the typical dose range. 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 codeine-containing products as follows.

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[1] Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.

[2] Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.

- Add a **BOXED WARNING** as follows to the beginning of the package insert.

WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (see WARNINGS – *Codeine Phosphate* - Death Related to Ultra-Rapid Metabolism of Codeine to Morphine).

- In the **CONTRAINDICATIONS** section, add the following information as the first contraindication.

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

- In the **WARNINGS** section, the following information should appear first.

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine
Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see **PRECAUTIONS -Nursing Mothers**).

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see **OVERDOSAGE**).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS**).

When prescribing codeine-containing drugs, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose.

- In the **PRECAUTIONS** section, (b) (4)

(b) (4)

- In the **PRECAUTIONS – Information for Patients** section, delete the following language.

(b) (4)

- In the **PRECAUTIONS – Information for Patients** section, replace the language deleted above with the following language.

Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid codeine metabolizer or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. As a result, codeine is contraindicated in all children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to

monitor for signs of respiratory depression (see **WARNINGS- Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**).

- In the **PRECAUTIONS – Nursing Mothers** subsection, delete the following language because that information is now included in the new warning information.

(b) (4)

- In the **PRECAUTIONS – Nursing Mothers** subsection, replace the existing cross-reference at the end of the paragraph regarding ultra-rapid metabolizers of codeine with the following cross-reference.

(see **WARNINGS- Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**)

- In the **PRECAUTIONS - Pediatric Use** subsection, add the following language at the beginning of the section.

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme CYP2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in these patients (see **WARNINGS - Death Related to Ultra-Rapid Metabolism of Codeine to Morphine and CONTRAINDICATIONS**).

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction and pay the required PAS fee as required by the Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), 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.

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 monetary 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) – 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, call Carrie Lemley, Labeling Project Manager at (240) 276-8986.

Sincerely,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

02/19/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

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

/s/

KEITH O WEBBER
05/10/2013