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**Subject: A Synopsis of the Elements of the S.T.E.P.S.[®]
Program**

Background

Thalomid[®] (thalidomide) and its Approval

Thalomid[®] (thalidomide) (Celgene, Corp.) was approved by the US FDA in July 1998 under the restricted distribution provisions of Subpart H, 21 CFR §314.520. Approval under subpart H restricted distribution requires that postmarketing restrictions are implemented to provide for the safe use of the drug product. Specifically, Subpart H states the following:

§ 314.520 Approval with restrictions to assure safe use.

- (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
 - (1) Distribution restricted to certain facilities or physicians with special training or experience; or
 - (2) Distribution conditioned on the performance of specified medical procedures.
- (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

The approved indications for Thalomid® are the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. The required risk management program instituted by Celgene Corporation for the distribution of Thalomid® is the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®).

Thalomid® Prescribing Patterns

The major specific safety concern for thalidomide is teratogenicity and the risk management goals are the prevention of fetal exposures to thalidomide. An evaluation of recent usage patterns of Thalomid® under the S.T.E.P.S.® program revealed that almost 90% of the prescribing of Thalomid® is for oncologic conditions. Between September 1998 and April 2003, approximately 77,000 patients were prescribed Thalomid® (a total of approximately 400,000 prescriptions). Of these 77,000 patients, approximately 4000 patients were females of childbearing potential. Evaluation of the distribution of Thalomid® recipients by gender finds a slight predominance of male patients. The mean age for patients receiving Thalomid® in the S.T.E.P.S.® program is approximately 65 years of age.

A Synopsis of the S.T.E.P.S.® Program

Elements of S.T.E.P.S.® Program

The S.T.E.P.S.® program includes a number of tools to manage the risks of Thalomid®. The key elements of the S.T.E.P.S.® program include the following:

- Product labeling informing of the risks of thalidomide and containing elements of the S.T.E.P.S.® program
- Required registration of all prescribers, patients, and pharmacists who prescribe, receive, or dispense Thalomid® (thalidomide)
- Six risk groups based on age, gender, and reproductive status
- A patient acknowledgement / informed consent form
- Authorization validation prior to dispensing Thalomid®
- A required telephonic survey (utilizes an interactive voice response system (IVR)) that patients and prescribers must complete.
- Required pregnancy testing in females of childbearing potential
- Compliance with measures to prevent pregnancy and thereby prevent fetal exposure to Thalomid®
- Educational materials – a brochure and a video tape
- Patient counseling
- Limiting prescriptions to a 28-day supply that is provided in blister packs with safety information on the blister card as well as prohibition of telephone prescriptions and automatic refills

- Distribution of Thalomid® from Celgene to registered pharmacies
- Any suspected fetal exposures to Thalomid must be reported immediately
- Quality assurance activities of the S.T.E.P.S.® program - ongoing evaluation of the S.T.E.P.S.® program

In the sections that follow further information is provided on the elements of the S.T.E.P.S.® program that are listed above.

Product Labeling

The Thalomid® product labeling provides Warnings regarding the teratogenicity of thalidomide, the elements of the patient acknowledgement / informed consent form, and describes other elements of the S.T.E.P.S.® program. The label explicitly states the requirement for enrollment in S.T.E.P.S.® prior to institution of drug therapy. Statements concerning risk to the fetus by mention of “birth defects”, “fetal abnormalities”, or “teratogenicity” if thalidomide is taken during pregnancy are present in several sections of the Thalomid® label. At the top of the Thalomid® label is a boxed Warning entitled “WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.” Overall, such statements are present in the following sections of the label: Warnings (including the boxed Warning), Contraindications, Precautions, and Adverse Reactions. The Thalomid® label refers to the S.T.E.P.S.® program with explicit mention of the requirement for enrollment prior to thalidomide therapy. The complete Thalomid® (thalidomide) package insert also provides additional information on Thalomid® including other information such as additional Warnings and Precautions, information on Adverse Events, Indications and Usage, and Dosage and Administration.

Required Registration of Prescribers, Patients, and Pharmacies

All prescribers, patients, and pharmacies are required to register in the S.T.E.P.S.® program in order to prescribe, receive, or dispense Thalomid®. Physician registration requires a DEA# or Social Security Number as well as the designation of a S.T.E.P.S.® coordinator for that prescriber (this may be the prescriber). The registration form is faxed to the prescriber and when completed faxed back to Celgene Corporation. A pharmacy registers by having a designated pharmacist complete a similar registration form that is returned to Celgene. (For patient registration information, please see “Patient Acknowledgement/ Informed Consent” below).

Six Risk Groups

The S.T.E.P.S.® program divides patients into six risk groups in order to provide risk group appropriate information to prevent fetal exposure to thalidomide. For example, adult females not of childbearing potential are required to participate in the Interactive Voice Response System (IVR) survey once every six months whereas females of childbearing potential (FCBP) are required to participate monthly.

The six risk groups are as follows:

- Adult females of childbearing potential
- Adult females not of childbearing potential
- Female children of childbearing potential
- Female children not of childbearing potential
- Adult males
- Male children

Patient Acknowledgement / Informed Consent Form

The risk group appropriate patient acknowledgement / informed consent form can be generated using computer software that is supplied with the materials for prescribers registered in the S.T.E.P.S.® program. Prescribers are expected to provide these risk group specific forms to the patient, provide counseling on the risks and benefits of therapy, provide mandatory contraceptive counseling, pregnancy testing for females of childbearing potential and then fax the completed acknowledgement / informed consent forms to Celgene Corporation. When computer generated forms cannot be used, risk group appropriate forms can be provided by fax to the prescriber. The patient is registered with S.T.E.P.S.® upon receipt of the acknowledgement / informed consent form by Celgene.

Authorization Validation

After the risk group appropriate patient acknowledgement / informed consent form has been completed and faxed to Celgene Corporation the patient is then instructed to complete the patient phone survey while the prescriber completes the physician phone survey. Upon completion of the survey, the physician obtains an authorization number that is placed on the prescription which the patient then presents to the pharmacist. Without the authorization number Thalomid® cannot be dispensed. (Please see below, IVR system).

Required Telephonic Survey Utilizing an IVR System

A brief, automated, telephone-based survey that utilizes IVR technology (IVR=interactive voice response system). The survey questions are tailored to each of the specific risk group as are the intervals for completing the required IVR surveys. All patient risk groups complete the survey with each 28-day interval, except for adult females not of childbearing potential who complete the IVR survey every 6 months. Prescribers complete the IVR survey with each prescription (maximum dispense of a 28-day supply). At the end of the successful completion of the prescriber survey a number to be written on prescription form is generated (the authorization number).

The risk group specific IVR survey is a series of 4 to 6 questions for each participant (Prescriber and Patient) intended to acquire essential information and to perform a focused query for at-risk behavior or program non-compliance. The prescriber and patient must answer all questions in the IVR survey appropriately before a Thalomid® prescription is “activated”. When a response to the IVR system signals an at-risk behavior, the prescriber or patient is transferred from the IVR system to a Celgene S.T.E.P.S.® intervention specialist for real-time intervention prior to dispensing of Thalomid® (specialists are available 8a-8p M-F & Sat).¹ The response that triggered the intervention is further addressed and remediated as appropriate.

If the patient and prescriber responses are appropriate to all questions in the IVR, the Thalomid® prescription is “activated.” Then a registered pharmacist can call the IVR system, enter the number from the prescription, and the pharmacist then receives authorization to dispense the “activated” Thalomid® prescription. To reflect the temporal restriction with regard to recent pregnancy testing. Thalomid® prescriptions are required to be filled within seven days of issue. Conventional methods (paper, fax, telephone) are available when the IVR cannot be used (paper forms are also available in fourteen languages). When a paper based process is used, the handling process is the same as for the IVR (i.e., real-time intervention).

Required Pregnancy Testing

Females of childbearing potential are required to have a negative pregnancy test within 24 hours prior to initiating Thalomid® therapy. Testing occurs weekly for the first 4 weeks, and then q-28 days thereafter while on Thalomid®, unless menses are irregular in which case pregnancy testing is performed on a biweekly basis. The prescriber enters the date and result of the last pregnancy test into the IVR system with each Thalomid prescription (i.e., every 28-days). Therapy

¹ Incorrect responses that occur at off-hours result in an inactivated prescription that is followed-up during hours of staffing.

with Thalomid® must be discontinued immediately if a pregnancy occurs in a patient receiving Thalomid® therapy.

Compliance with Measures to Prevent Pregnancy

Females of childbearing potential must use at least one highly effective method of birth control and one additional method of birth control.² These methods of contraception must be initiated at least four weeks before beginning Thalomid® therapy, must be continued during Thalomid® therapy, and continued for four weeks following discontinuation of Thalomid® therapy. Females of childbearing potential must use these birth control methods unless the patient completely abstains from heterosexual sexual contact. Male patients receiving Thalomid® must agree to abstain from heterosexual sexual contact or use a latex condom when he engages in sexual contact with a woman who can become pregnant or who is pregnant.

Educational Materials – Brochure and Video Tape

Patients must review the Thalomid® patient brochure and/or view the videotape regarding the safe use of Thalomid®.

Patient Counseling

Patients are to receive counseling to review the safe use of Thalomid® at the time of initial S.T.E.P.S.® enrollment and subsequently at each prescription refill.

Limiting Prescriptions to a 28-day Supply

Thalomid® prescriptions are limited to a duration of 28-days to allow for appropriate interval follow-up. Telephone prescriptions are not permitted. A new prescription is required for further dispensing (i.e. automatic refills are not permitted).

Distribution of Thalomid® from Celgene to Registered Pharmacies

Thalomid® is directly shipped from Celgene to registered pharmacies. This allows Celgene to compare the amount of Thalomid® shipped to pharmacies with the amount of Thalomid® that specific pharmacies have been authorized to dispense.

² Highly effective = hormonal, IUD, tubal ligation, partner's vasectomy; Effective = latex condom, diaphragm, cervical cap

Any Suspected Fetal Exposures to Thalomid Must be Reported Immediately

Prescribers must report any suspected fetal exposure to Thalomid immediately to the FDA and Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The label provides the FDA MedWatch phone number (800-FDA-1088) and also includes an “800” number for Celgene Corporation. Any suspected fetal exposures to Thalomid® also receive additional follow-up.

Quality Assurance Activities of the S.T.E.P.S.® Program

Ongoing assessments of the S.T.E.P.S.® program and a separate voluntary follow-up survey are performed as part of the quality assurance activities of the S.T.E.P.S.® program.