CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER: ANDA 075945/S-014

Name: Amnesteem (Isotretinoin Capsules USP) 10 mg, 20 mg, 40 mg

Sponsor: Genpharm, Inc.

Approval Date: March 25, 2010
**CONTENTS**

**Reviews / Information Included in this Review**

<table>
<thead>
<tr>
<th>Approval Letter</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Labeling Review</td>
<td>X</td>
</tr>
<tr>
<td>Medical Review</td>
<td></td>
</tr>
<tr>
<td>Chemistry Reviews</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Reviews</td>
<td></td>
</tr>
<tr>
<td>Statistical Review</td>
<td></td>
</tr>
<tr>
<td>Microbiology Reviews</td>
<td></td>
</tr>
<tr>
<td>Administrative &amp; Correspondence Documents</td>
<td>X</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
ANDA 075945/S-014

APPROVAL LETTER
Mylan Pharmaceuticals Inc.
Attention: Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your supplemental new drug application dated March 4, 2010, submitted pursuant to 21 CFR 314.70(c)(6) [Supplement - Changes Being Effected] regarding your abbreviated new drug application for Amnesteem® (Isotretinoin Capsules USP), 10 mg, 20 mg, and 40 mg.

This supplemental application provides for revised insert and medication guide labeling to be in accordance with the most recently approved labeling for the reference listed drug, Accutane® Capsules (NDA 18-662/S-060: Approved February 01, 2010).

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Regards,

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA-75945</td>
<td>SUPPL-14</td>
<td>GENPHARM INC</td>
<td>ISOTRETINOIN</td>
</tr>
</tbody>
</table>

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

/s/

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JOHN F GRACE
03/25/2010
for Wm Peter Rickman
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 075945/S-014

LABELING
**Amnesteem® (Isotretinoin Capsules USP)**

**INDICATIONS AND USAGE:** Severe Recalcitrant Nodular Acne:
- Amnesteem is indicated in the management of severe nodular acne that is resistant to conventional therapy (see WARNINGS). It is also indicated in patients who have failed to respond or whose condition has deteriorated on conventional therapy (see WARNINGS). Amnesteem is indicated for the treatment of patients 12 to 17 years of age who have failed to respond to or whose condition has deteriorated on conventional therapy (see WARNINGS).

**DOSAGE AND ADMINISTRATION:**
- The dose of Amnesteem is 10 or 30 mg/day, given in divided doses twice daily (see WARNINGS). The dose is titrated upward from a starting dose of 10 mg/day to a maintenance dose of 10 mg/day or 30 mg/day depending on the patient's response and tolerability (see WARNINGS).
- The maintenance dose is then given twice daily for as long as the patient continues to respond to therapy (see WARNINGS).

**CONTRAINDICATIONS:**
- Amnesteem is contraindicated in patients who are pregnant (see WARNINGS). It is also contraindicated in patients who have a known history of hypersensitivity to any component of Amnesteem (see WARNINGS).

**WARNINGS:**
- Pregnancy: Amnesteem is contraindicated in women who are or may become pregnant (see WARNINGS).
- Patients with a known history of liver dysfunction, and/or increased serum liver enzyme levels may be at increased risk (see WARNINGS). Patients with a history of depression, and/or increased serum liver enzyme levels may be at increased risk (see WARNINGS).
- Patients with a history of depression, and/or increased serum liver enzyme levels may be at increased risk (see WARNINGS).
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**PRECAUTIONS:**
- Patients with a history of depression, and/or increased serum liver enzyme levels may be at increased risk (see WARNINGS).
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**ADVERSE REACTIONS:**
- Amnesteem is associated with the development of ischemic and non-ischemic retinal changes, and these changes may be reversible and may persist (see WARNINGS). Amnesteem is associated with the development of ischemic and non-ischemic retinal changes, and these changes may be reversible and may persist (see WARNINGS). Amnesteem is associated with the development of ischemic and non-ischemic retinal changes, and these changes may be reversible and may persist (see WARNINGS). Amnesteem is associated with the development of ischemic and non-ischemic retinal changes, and these changes may be reversible and may persist (see WARNINGS).

**NURSING MOTHERS:**
- There are no adequate and well-controlled studies in pregnant women. It is not known whether Amnesteem is excreted in human milk. Caution should be exercised when Amnesteem is administered to a nursing mother (see WARNINGS). Amnesteem may cause an increased risk of thrombosis in patients who are taking oral contraceptives (see WARNINGS).

**ADDITIONAL INFORMATION:**
- Patients should be informed not to donate blood during therapy and for one month following discontinuation of therapy (see WARNINGS). Patients should be informed that it is essential to follow oral contraception guidelines while taking Amnesteem (see WARNINGS). Patients should be informed that if they are planning to become pregnant, they should use an effective contraceptive method for 1 month before and 1 month after discontinuing therapy (see WARNINGS). Patients should be informed that they should use an effective contraceptive method for 1 month before and 1 month after discontinuing therapy (see WARNINGS).

**REPRODUCIBILITY OF RESULTS:**
- The in vitro and in vivo reproducibility of results with Amnesteem is not known (see WARNINGS). Amnesteem has been shown to be effective in the treatment of severe nodular acne (see WARNINGS). Amnesteem has been shown to be effective in the treatment of severe nodular acne (see WARNINGS). Amnesteem has been shown to be effective in the treatment of severe nodular acne (see WARNINGS). Amnesteem has been shown to be effective in the treatment of severe nodular acne (see WARNINGS).
MEDICATION GUIDE
AMNESTEEM (AM-NES-TEAM) (Isotretinoin Capsules, USP)

Read the Medication Guide that comes with Amnesteem before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Amnesteem?
- Amnesteem® (Isotretinoin Capsules, USP) is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics.
- Because Amnesteem can cause birth defects, Amnesteem is only for patients who can understand and agree to carry out all of the instructions in the iPLEDGE program.
- Amnesteem may cause serious mental health problems.

1. Birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby and early (premature) births. Female patients who are pregnant or who plan to become pregnant must not take Amnesteem. Female patients must not get pregnant:
   - for one month before starting Amnesteem
   - while taking Amnesteem
   - for one month after stopping Amnesteem.

2. Serious mental health problems. Amnesteem may cause:
   - depression
   - psychosis (seeing or hearing things that are not real)
   - suicide. Some patients taking Amnesteem have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives.

Stop Amnesteem and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:
- start to feel sad or have crying spells
- lose interest in activities you once enjoyed
- sleep too much or have trouble sleeping
- become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- have a change in your appetite or body weight
- have trouble concentrating
- feel like you have no energy
- have feelings of worthlessness or guilt
- start having thoughts about hurting yourself or taking your own life (suicidal thoughts)
- start acting on dangerous impulses
- start seeing or hearing things that are not real

After stopping Amnesteem, you may also need follow-up mental health care if you had any of these symptoms.

What is Amnesteem?
Amnesteem is a medicine taken by mouth to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. Amnesteem can cause serious side effects (see “What is the most important information I should know about Amnesteem?”). Amnesteem can only be:
- prescribed by doctors that are registered in the iPLEDGE program
- dispensed by a pharmacy that is registered with the iPLEDGE program
- given to patients who are registered in the iPLEDGE program and agree to do everything required in the program

What is severe nodular acne?
Severe nodular acne is when many red, swollen, tender lumps form in the skin. These can be the size of pencil erasers or larger. If untreated, nodular acne can lead to permanent scars.

Who should not take Amnesteem?
- Do not take Amnesteem if you are pregnant, plan to become pregnant or become pregnant during Amnesteem treatment. Amnesteem causes severe birth defects. See “What is the most important information I should know about Amnesteem?”
- Do not take Amnesteem if you are allergic to anything in it. See the end of this Medication Guide for a complete list of ingredients in Amnesteem.

What should I tell my doctor before taking Amnesteem?
Tell your doctor if you or a family member has any of the following health conditions:
- mental problems
- asthma
- liver disease
- diabetes
- heart disease
- bone loss (osteoporosis) or weak bones
- an eating problem called anorexia nervosa (where people eat too little)
- food or medicine allergies

Tell your doctor if you are pregnant or breast-feeding. Amnesteem must not be used by women who are pregnant or breast-feeding.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Amnesteem and certain other medicines can interact with each other, sometimes causing serious side effects. Especially tell your doctor if you take:
- Vitamin A supplements. Vitamin A in high doses has many of the same side effects as Amnesteem. Taking both together may increase your chance of getting side effects.
- Tetracycline antibiotics. Tetracycline antibiotics taken with Amnesteem can increase the chances of getting increased pressure in the brain.
- Progestin-only birth control pills (mini-pills). They may not work while you take Amnesteem. Ask your doctor or pharmacist if you are not sure what type you are using.
- Dilantin (phenytoin). This medicine taken with Amnesteem may weaken your bones.
- Corticosteroid medicines. These medicines taken with Amnesteem may weaken your bones.
- St. John’s Wort. This herbal supplement may make birth control pills work less effectively.

These medicines should not be used with Amnesteem unless your doctor tells you it is okay.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take any new medicine without talking with your doctor.

How should I take Amnesteem?
- You must take Amnesteem exactly as prescribed. You must also follow all the instructions of the iPLEDGE program. Before prescribing Amnesteem, your doctor will:
  - explain the iPLEDGE program to you
  - have you sign the Patient Information/Informed Consent form (for all patients). Female patients who can get pregnant must also sign another consent form.

You will not be prescribed Amnesteem if you cannot agree to or follow all the instructions of the iPLEDGE program.

- You will get no more than a 30 day supply of Amnesteem at a time. This is to make sure you are following the Amnesteem iPLEDGE program. You should talk with your doctor each month about side effects.
- The amount of Amnesteem you take has been specially chosen for you. It is based on your body weight, and may change during treatment.
- Take Amnesteem 2 times a day with a meal, unless your doctor tells you otherwise. Swallow your Amnesteem capsules whole with a full glass of liquid. Do not chew or suck on the capsule. Amnesteem can hurt the tube that connects your mouth to your stomach (esophagus) if it is not swallowed whole.
- If you miss a dose, just skip that dose. Do not take two doses at the same time.
- If you take too much Amnesteem or overdose, call your doctor or poison control center right away.

- Your acne may get worse when you first start taking Amnesteem. This should last only a short while. Talk with your doctor if this is a problem for you.
- You must return to your doctor as directed to make sure you don’t have signs of serious side effects. Your doctor may do blood tests to check for serious side effects from Amnesteem. Female patients who can get pregnant will get a pregnancy test each month.
- Female patients who can get pregnant must agree to use two separate forms of effective birth control at the same time one month before, while taking and for one month after taking Amnesteem. You must access the iPLEDGE system to answer questions about the program requirements and to enter your two chosen forms of birth control. To access the iPLEDGE system, go to www.ipledgeprogram.com or call 1-866-495-0654.
- You must talk about effective birth control methods with your doctor or go for a free visit to talk about birth control with another doctor or family planning expert. Your doctor can arrange this free visit, which will be paid for by the company that makes Amnesteem.

If you have sex at any time without using two forms of effective birth control, get pregnant or miss your expected period, stop using Amnesteem and call your doctor right away.

What should I avoid while taking Amnesteem?
- Food or medicine allergies
- Vitamin A supplements
- Tetracycline antibiotics
- Progestin-only birth control pills (mini-pills)
- Dilantin (phenytoin)
- Corticosteroid medicines
- St. John’s Wort

Do not take Amnesteem:
- If you are allergic to any of the ingredients in Amnesteem.
- If you have had a severe reaction to Amnesteem in the past.
- If you have taken Amnesteem in the past and had a reaction after the first dose.
- If you are allergic to anything in Amnesteem.
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- If you are allergic to anything in Amnesteem.

Do not give Amnesteem to children.

If you take Amnesteem:
- You must access the iPLEDGE system to answer questions about the program requirements and to enter your two chosen forms of birth control. To access the iPLEDGE system, go to www.ipledgeprogram.com or call 1-866-495-0654.
- You must talk about effective birth control methods with your doctor or go for a free visit to talk about birth control with another doctor or family planning expert. Your doctor can arrange this free visit, which will be paid for by the company that makes Amnesteem.

If you have sex at any time without using two forms of effective birth control, get pregnant or miss your expected period, stop using Amnesteem and call your doctor right away.

What should I avoid while taking Amnesteem?
What are the possible side effects of Amnesteem?

- **bone and muscle problems.** Amnesteem can affect bones, muscles, and ligaments and may decrease your ability to see in the dark. These organs include the liver, pancreas, bowel (intestines), and yellow iron oxide paste. Gelatin capsules contain glycerin, with the following dye systems: Rhodamine 6G, Red Iron Oxide, and yellow iron oxide paste. Gelatin capsules contain glycerin, with the following dye systems: Rhodamine 6G, Red Iron Oxide, and yellow iron oxide paste.
- **heart problems.** Amnesteem can raise the level of fats and cholesterol in your blood. This can be a serious problem. Return to your doctor for blood tests to check your lipids and to get any needed treatment. These problems usually go away when Amnesteem treatment is finished.
- **vision problems.** Amnesteem may affect your ability to see in the dark. This condition usually clears up after you stop taking Amnesteem, but it may be permanent. Other serious eye effects can occur. Stop taking Amnesteem and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant. If you wear contact lenses, you may have trouble wearing them while taking Amnesteem and after treatment.
- **liver problems.** Amnesteem can cause blood sugar problems including diabetes. Tell your doctor if you are very thirsty or urinate a lot. Decreased red and white blood cells. Call your doctor if you have trouble breathing, faint or feel weak.
- **The common, less serious side effects of Amnesteem** are dry skin, chapped lips, dry eyes and dry nose that may lead to nosebleeds. Call your doctor if you get any side effect that bothers you or that does not go away.

These are not all of the possible side effects with Amnesteem. Your doctor or pharmacist can give you more detailed information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Amnesteem?

- Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from light.
- Keep Amnesteem and all medicines out of the reach of children.

Amnesteem may affect your ability to see in the dark. This condition usually clears up after you stop taking Amnesteem, but it may be permanent. Other serious eye effects can occur. Stop taking Amnesteem and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant.

If you wear contact lenses, you may have trouble wearing them while taking Amnesteem and after treatment.

Amnesteem can cause blood sugar problems including diabetes. Tell your doctor if you are very thirsty or urinate a lot.

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Amnesteem may affect your ability to see in the dark. This condition usually clears up after you stop taking Amnesteem, but it may be permanent. Other serious eye effects can occur. Stop taking Amnesteem and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant.

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Labeling Review Branch
Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review

Application Number:  75-945/S-014

Name of Drug:  Amnesteem® (Isotretinoin Capsules USP), 10 mg, 20 mg, and 40 mg.
Applicant:  Mylan Pharmaceuticals, Inc.

Material Reviewed:
Submission Date:  March 4, 2010

Background and Summary
Model labeling:  Accutane Capsules (NDA 18-662/S-060: Approved February 01, 2010)
This supplemental new drug application provides for revisions to question 12 of the Patient Information/Informed Consent About Birth Defects. It also provides for changes to the to the “WARNINGS” section to include new information regarding serious skin reactions.

Review

REVISIONS:  Same as the reference listed drug, Accutane Capsules:  Approved February 01, 2010.

Package insert/Medication Guide – See attached pages for revisions

Recommendation

Labeling: Satisfactory as submitted electronically March 4, 2010

Approve labeling supplement.

{see appended electronic signature}

Beverly Weitzman
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

John Grace
Team Leader
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
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</tbody>
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/s/

BEVERLY WEITZMAN
03/23/2010

JOHN F GRACE
03/25/2010
APPLICATION NUMBER:
ANDA 075945/S-014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
March 4, 2010

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED
(LABELING INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Amnesteem® (Isotretinoin Capsules, USP) 10 mg, 20 mg and 40 mg ANDA 075945
(Labeling Revisions Pursuant to the CDER Internet Posting Dated February 1, 2010)

Dear Mr. Buehler:

We wish to supplement the above referenced Abbreviated New Drug Application (ANDA) with a revised final printed outsert (ISOT:R1/MG:ISOT:R1, February 2010) pursuant to CDER Internet Posting dated February 1, 2010 (NDA 018662/S-060) which contained labeling revisions for the innovator product, ACCUTANE® (Hoffmann-La Roche Inc.). A copy of the CDER Internet Posting letter dated February 1, 2010 is provided in Section 1.4.4 for the reviewer’s reference. A copy of the Innovator’s labeling approved on February 1, 2010 is included in Section 1.14.3.2. Editorial revisions have also been made to the final printed outsert to be consistent with Mylan’s current standard format. A side-by-side comparison of Mylan’s proposed final printed final printed outsert to the currently approved outsert is provided in Section 1.14.1.2.

In accordance with the Agency’s Guidance Providing Regulatory Submissions in Electronic Format – Content of Labeling (April 2005), Structured Product Labeling (SPL) for Amnesteem (Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg is provided in Section 1.14.2.3. As a review aid, Microsoft Word versions have also been provided for the proposed labeling components.

The revised outsert will be issued for production use in approximately 30 days from the date of this supplement.
This supplement is being submitted through the FDA’s Electronic Submissions Gateway. Please note that Mylan submitted a letter of Non-Repudiation on April 17, 2006. Should you have any questions regarding this supplement, please contact the undersigned by telephone at (304) 599-2595, ext. 6551, via facsimile at (304) 285-6407 or email at wayne.talton@mylanlabs.com.

Sincerely,

[Signature]

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/bk