PACKAGING FOR ALITRE Tin oIN

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ABSTRACT

The present invention relates to the use of an oxygen absorber and silica gel desiccant in a vacuum-sealed pack for the reduction or prevention of oxidative degradation of alitretino in.
PACKAGING FOR ALITRETONIN

FIELD OF THE INVENTION

[0001] The present invention relates to the use of an oxygen absorber and silica gel desiccant in a vacuum-sealed pack for the reduction or prevention of oxidative degradation of alitretinoin.

BACKGROUND OF THE INVENTION

[0002] Alitretinoin is a first generation retinoid. The chemical name of alitretinoin is 9-cis retinoic acid or (2E,4E,6Z,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoic acid and the structural formula is as follows:

![Formula I]

[0003] The European Public Assessment Report (EPAR) scientific discussion document on alitretinoin published by the European Medicines Agency (accessible at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000279/WC500038707.pdf, page 2) discloses that in alitretinoin, decomposition was extensive in the presence of oxygen giving rise to a large number of impurities. Drug degradation often limits shelf life or may render a drug unmarketable. Therefore, such drugs are required to be stored in the absence of oxygen or under a condition that the oxygen content is very small. To achieve this, nitrogen may be filled into a container or a package. However, once such container is opened or the package is unwrapped, air flows in and the quality cannot be prevented from deterioration.

[0004] In the pharmaceutical industry, there have been reports of using oxygen absorbers to stabilize drugs. For example, Japanese Patent No. JP 59-176247 discloses a method for preventing the decomposition of water-soluble azulene of Formula II by packing and sealing it in a glass impermeable container together with a deoxidant. U.S. Pat. No. 6,007,529 discloses a flexible transparent container for the improved storage of oxygen sensitive parenterally administrable agents that is comprised of an inner primary container that is enclosed in an oxygen impermeable outer envelope with an oxygen absorber capable of consuming all residual oxygen after the outer envelope is sealed.

[0005] PCT Publication No. WO 2006/008651 discloses a package to protect pharmaceuticals, e.g., atorvastatin, which comprises a bottle, a deoxidant disposed within the first sub-container, and a self-activated metal based oxygen absorber disposed within the second sub-container. U.S. Publication No. 2005/0268573 relates to a method for packaging a sterile article that comprises providing a container; placing the article into the interior of the container; exposing the permeable portion of the container to the exterior environment; and removing the sterilizing gas. U.S. Publication No. 2009/0071855 discloses a vacuum-sealed pack comprising an amorphous statin or a pharmaceutical composition thereof and at least one stabilizer, for example, an oxygen absorber, a moisture absorber, or a combination thereof.

[0006] There is a need to provide a packaging system for alitretinoin for the reduction or prevention of its oxidative degradation.

SUMMARY OF THE INVENTION

[0007] In one aspect, there is provided a method for the reduction or prevention of oxidative degradation of alitretinoin using an oxygen absorber and a silica gel desiccant in a vacuum-sealed pack.

[0008] In another aspect, there is provided a vacuum-sealed pack comprising alitretinoin, an oxygen absorber and a silica gel desiccant.

[0009] In yet another aspect, there is provided a vacuum-sealed pack comprising a pharmaceutical composition comprising alitretinoin, an oxygen absorber, and a silica gel desiccant.

DETAILED DESCRIPTION OF THE INVENTION

[0010] In one aspect, there is provided a method for the reduction or prevention of oxidative degradation of alitretinoin comprising an oxygen absorber and a silica gel desiccant in a vacuum-sealed pack.

[0011] In another aspect, there is provided a vacuum-sealed pack comprising alitretinoin, an oxygen absorber and a silica gel desiccant.

[0012] In yet another aspect, there is provided a vacuum-sealed pack which includes a pharmaceutical composition comprising alitretinoin, an oxygen absorber, and a silica gel desiccant.

[0013] The term “vacuum-sealed pack”, as used herein, refers to a low density polyethylene (LDPE) bag that is twisted and tied with a plastic fastener under nitrogen. This bag is packed into a middle bag of polyester/LDPE, a vacuum is applied to the middle bag, and it is heat sealed. The sealed middle bag is packed into a polyester/aluminum/polyester/LDPE bag. Vacuum is applied to the polyester/aluminum/polyester/LDPE bag and it is then heat sealed.

[0014] The term “oxygen absorber”, as used herein, is a material capable of absorbing oxygen from the surrounding atmosphere. Oxygen absorbers can be inorganic metal based oxygen absorbers; ascorbic acid based absorbers; enzymatic absorbers; or polymer based oxygen absorbers. Examples of specific oxygen absorbers include, but are not limited to, O-Buster®, FreshPax®, Ageless®, StabilOx® or ZIPiT™.

[0015] Stability studies of alitretinoin were conducted by loading alitretinoin samples at various stability conditions,
for example, at 25±2°C./60±5% relative humidity (RH) and 40±2°C./75±5% RH in the absence or presence of an oxygen absorber and a silica desiccant for 1 month, 2 months, 3 months, or 6 months. The stability studies were performed on a stability incubator (for accelerated stability studies, Hotpack was used and for real time stability studies, NuAire® was used). The degradation products were identified using an Agilent® 1100 series HPLC system.

[0016] The “pharmaceutical composition”, as used herein, includes both capsule and gel forms.

[0017] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. Examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention.

EXAMPLES

Example 1

Stability Studies of Alitretinoin at 25±2°C./60±5% RH and 40±2°C./75±5% RH in the Absence of Oxygen Absorber and Silica Gel Desiccant

[0018] Alitretinoin was packed in a LDPE bag. The bag was twisted and tied with a plastic fastener under nitrogen. The LDPE bag was placed into a middle bag of polyester/LDPE and vacuum was applied to the middle bag and then it was heat sealed. The sealed middle bag was packed into a polyester/aluminum/polyester/LDPE bag. Vacuum was applied to this bag and then it was heat sealed. The vacuum-sealed pack was loaded on stability at stations 40±2°C. and 75±5% RH (accelerated) and 25±2°C. and 60±5% RH. The results are presented in Table 1.

<table>
<thead>
<tr>
<th>Impurities</th>
<th>Initial</th>
<th>2M/25 ± 2°C/60 ± 5% RH</th>
<th>1M/40 ± 2°C/75 ± 5% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Oxo-alitretinoin</td>
<td>0.026</td>
<td>0.123</td>
<td>0.176</td>
</tr>
<tr>
<td>4-Hydroxy alitretinoin</td>
<td>0.007</td>
<td>0.113</td>
<td>0.161</td>
</tr>
<tr>
<td>5,6-Epoxy alitretinoin</td>
<td>0.001</td>
<td>0.058</td>
<td>0.048</td>
</tr>
<tr>
<td>Total related substances</td>
<td>0.405</td>
<td>0.892</td>
<td>1.146</td>
</tr>
</tbody>
</table>

Example 2

Stability Studies of Alitretinoin at 25±2°C./60±5% RH in the Presence of Oxygen Absorber (Stabilox®) and Silica Gel Desiccant

[0019] Alitretinoin was packed in a LDPE bag. The bag was twisted and tied with a plastic fastener under nitrogen. The LDPE bag was placed into a middle bag of polyester/LDPE along with an oxygen absorber. A vacuum was applied to the middle bag and then it was heat sealed. The sealed middle bag was packed into a polyester/aluminum/polyester/LDPE bag along with silica gel as a desiccant. Vacuum was applied to this bag and it was then heat sealed. The vacuum-sealed pack was loaded on stability at 25±2°C. and 60±5% RH. The results are presented in Table 2.

<table>
<thead>
<tr>
<th>Impurities</th>
<th>Initial</th>
<th>3M/25 ± 2°C/60 ± 5% RH</th>
<th>6M/25 ± 2°C/60 ± 5% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Oxo-alitretinoin</td>
<td>0.002</td>
<td>0.003</td>
<td>0.004</td>
</tr>
<tr>
<td>4-Hydroxy alitretinoin</td>
<td>ND*</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>5,6-Epoxy alitretinoin</td>
<td>0.006</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>Total related substances</td>
<td>0.165</td>
<td>0.198</td>
<td>0.183</td>
</tr>
</tbody>
</table>

Example 3

Stability Studies of Alitretinoin at 40±2°C./75±5% RH in the Presence of Oxygen Absorber (Stabilox®) and Silica Gel Desiccant

[0020] Alitretinoin was packed in a LDPE bag; the bag was twisted and tied with a plastic fastener under nitrogen. It was placed into a middle bag of polyester/LDPE along with an oxygen absorber. Vacuum was applied to the middle bag and then it was heat sealed. The vacuum-sealed pack was loaded on stability at 40±2°C. and 75±5% RH. The results are presented in Table 3.

<table>
<thead>
<tr>
<th>Impurities</th>
<th>Initial</th>
<th>1M/40 ± 2°C/5% RH</th>
<th>2M/40 ± 2°C/5% RH</th>
<th>3M/40 ± 2°C/5% RH</th>
<th>6M/40 ± 2°C/5% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Oxo-alitretinoin</td>
<td>0.002</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>4-Hydroxy alitretinoin</td>
<td>ND*</td>
<td>0.003</td>
<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>5,6-Epoxy alitretinoin</td>
<td>0.006</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>Total related substances</td>
<td>0.165</td>
<td>0.173</td>
<td>0.173</td>
<td>0.173</td>
<td>0.173</td>
</tr>
</tbody>
</table>

[0021] From the results tabulated in Table 2 and Table 3, it has been concluded that in the presence of an oxygen absorber and a silica gel desiccant, alitretinoin showed no increase in oxidative impurities.

We claim:

1. A method for the reduction or prevention of oxidative degradation of alitretinoin comprising an oxygen absorber and a silica gel desiccant in a vacuum-sealed pack.

2. A vacuum-sealed pack comprising alitretinoin, an oxygen absorber and a silica gel desiccant.
3. A vacuum-sealed pack comprising a pharmaceutical composition which includes alitretinoin, an oxygen absorber, and a silica gel desiccant.

4. The vacuum-sealed pack of claim 1, 2, or 3, wherein the oxygen absorber is an inorganic metal based oxygen absorber; an ascorbic acid based absorber; an enzymatic absorber; or a polymer based oxygen absorber.

5. The vacuum-sealed pack of claim 1, 2, or 3, wherein the oxygen absorber is StabilOx®.