(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 April 2013 (25.04.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/057724 A1

(51) **International Patent Classification**:
B65D 77/04 (2006.01) ***B65D 81/26*** (2006.01)
B65D 81/20 (2006.01) ***A61K 31/02*** (2006.01)

(21) **International Application Number**:
PCT/IB2012/055762

(22) **International Filing Date**:
19 October 2012 (19.10.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
3019/DEL/2011 21 October 2011 (21.10.2011) IN

(71) **Applicant**: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) **Inventors**: **JAYACHANDRA, Suresh, Babu**; C-237, Phase - I, Sushant Lok, Gurgaon, Haryana 122002 (IN). **SINGH, Tarun, Kumar**; 485, Eldeco II, Abhishek, SGP-GI Road, Lucknow, Uttar Pradesh 226015 (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/057724 A1

(54) **Title**: PACKAGING FOR ALITRETINOIN

(57) **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 alitretinoin.

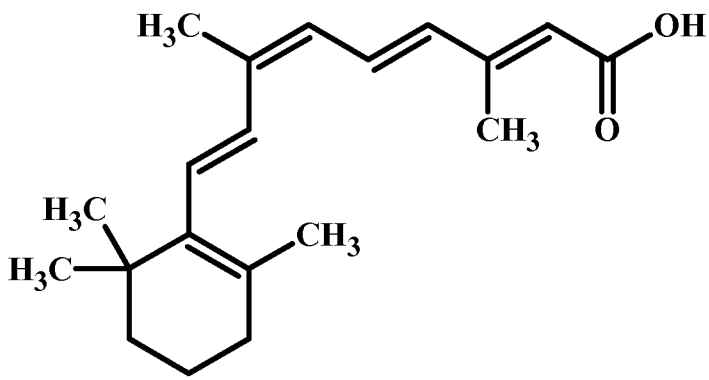
PACKAGING FOR ALITRETINOIN

Field of the Invention

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

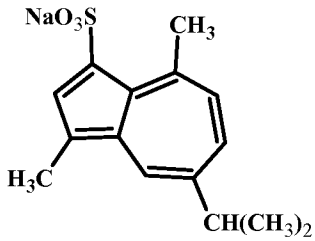
Alitretinoin is a first generation retinoid. The chemical name of alitretinoin is 9-cis retinoic acid or (2*E*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatraenoic acid and the structural formula is as follows:



Formula I

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.

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 azunole of Formula II



Formula II

by packing and sealing it in a glass impermeable container together with a deoxidant. U.S. Patent 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.

PCT Publication No. WO 2006/008651 discloses a package to protect pharmaceuticals, *e.g.*, atorvastatin, which comprises a bottle, a desiccant 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.

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

Summary of the Invention

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.

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

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

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.

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

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.

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.

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 ZPTJ™.

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.

The "pharmaceutical composition", as used herein, includes both capsule and gel forms.

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

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 1:

Impurities	Initial	2M/25±2°C/60±5% RH	1M/40±2°C/75±5% RH
4-Oxo-alitretinoin	0.026	0.123	0.176
	0.024	0.156	0.170
	0.012	0.063	0.052
4-Hydroxy alitretinoin	0.007	0.113	0.161
	0.009	0.156	0.160
	0.001	0.058	0.048
5,6-Epoxy alitretinoin	0.021	0.268	0.362
	0.049	0.376	0.380
	0.018	0.142	0.114

Total related substances	0.403	0.892	1.146
	0.411	1.128	1.181
	0.351	0.537	0.403

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

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 2:

Impurities	**Initial**	**3M/25±2°C/60±5% RH**	**6M/25±2°C/60±5% RH**
4-Oxo-alitretinoin	0.002	0.003	0.004
	0.003	0.002	0.004
	0.003	0.002	0.003
4-Hydroxy alitretinoin	ND*	0.003	0.002
	0.002	ND*	0.003
	ND*	ND*	0.002
5,6-Epoxy alitretinoin	0.006	0.008	0.006
	0.009	0.008	0.008
	0.006	0.005	0.005
Total related substances	0.165	0.198	0.183
	0.189	0.195	0.193
	0.173	0.179	0.167

*ND = not detected

Example 3: Stability Studies of Alitretinoin at 40±2°C/75±5%RH in the Presence of Oxygen Absorber (Stabilox®) and Silica Gel Desiccant

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.

This 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 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 3:

Impurities	**Initial**	**1M/40±2°C/ 75±5% RH**	**2M/40±2°C/ 75±5% RH**	**3M/40±2°C/ 75±5% RH**	**6M/40±2°C/ 75±5% RH**
4-Oxo-alitretinoin	0.002	0.004	0.003	0.003	0.003
	0.003	0.003	0.003	0.004	0.004
	0.003	0.003	0.002	0.003	0.003
4-Hydroxy alitretinoin	ND*	ND*	0.004	0.002	0.002
	0.002	ND*	0.003	0.003	0.002
	ND*	ND*	0.002	0.002	0.002
5,6-Epoxy alitretinoin	0.006	0.008	0.010	0.008	0.006
	0.009	0.008	0.008	0.010	0.007
	0.006	0.006	0.007	0.006	0.006
Total related substances	0.165	0.173	0.191	0.192	0.175
	0.189	0.182	0.192	0.205	0.188
	0.173	0.160	0.180	0.177	0.167

*ND = not detected

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 claims 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 claims 1, 2, or 3, wherein the oxygen absorber is StabilOx®.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/055762

A. CLASSIFICATION OF SUBJECT MATTER
INV. B65D77/04 B65D81/20 B65D81/26 A61K31/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B65D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/024946 A1 (RANBAXY LAB LTD [IN]; MUNSHI ANINDYA [IN]; BHARGAVA RAHUL [IN]) 26 February 2009 (2009-02-26) page 2, lines 1-3 page 2, line 13 - page 3, line 6 page 4, lines 1-3 page 5, lines 12-23; figure 1 -----	1-5
A	US 2009/249747 A1 (NISHIURA TAKAYUKI [JP] ET AL) 8 October 2009 (2009-10-08) the whole document -----	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2013	21/02/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Leijten, René

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/055762

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009024946 A1	26-02-2009	NONE	
US 2009249747 A1	08-10-2009	CN 101549781 A	07-10-2009
		DE 102009009035 A1	08-10-2009
		JP 4466756 B2	26-05-2010
		JP 2009248976 A	29-10-2009
		TW 200944433 A	01-11-2009
		US 2009249747 A1	08-10-2009