DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DOCKETS TRANSMITTAL MEMO

0431 '03 JAN 27 P2:22

™Date: JAN 23 2003

From: Consumer Safety Officer, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: 3-Acetyl-7-Oxo-dehydroepiandrosterone (7-Keto™DHEA)

Firm: Perrigo Company

Date Received by FDA: 7/29/02

90-Day Date: 10/27/02

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Gloria Chang

Gloria Chang, R.Ph./Interdisciplinary Scientist

Attachments

95-0316

RPT148

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

OCT 4 2002

Dave Jespersen
Director of Technical Services
Perrigo
515 Eastern Avenue
Allegan, Michigan 49010

Dear Mr. Jespersen:

This is to inform you that the notification, dated July 25, 2002, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on July 29, 2002. Your notification concerns the substance, 3-Acetyl-7-Oxo-dehydroepiandrosterone (7-Keto™DHEA), that you assert is a new dietary ingredient. You state that the dietary supplement will contain 100 mg of 3-Acetyl-7-Oxo-Dehyroepiandrosterone per tablet and the suggested use will be for adults up to two times per day.

In accordance with 21 C.F.R. 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. Please note that the acceptance of this notification for filing is only a procedural matter in accordance with 21 CFR 190.6(c) acknowledging FDA's receipt of your notification. Further, if we find that the information submitted is incomplete or additional substantive information is needed or submitted, the effective filing date may be reset (i.e., assigned a new filing date) subject to the date that we receive the complete information either as an amendment to the notification or as a new complete notification. FDA will notify the manufacturer of the new filing date.

You should also be aware that for 75 days after the effective filing date, you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains 3-Acetyl-7-Oxo-Dehydroepiandrosterone (7-Keto™DHEA).

Please note that FDA's failure to respond to a notification within or after the 75-day period does not constitute a finding by the agency that the new dietary ingredient or the dietary supplement that contains the new dietary ingredient is safe or is not adulterated under section 402 of the act. (21 CFR 190.6(5)(f)) Further, FDA is not precluded from taking action in the future against a dietary supplement containing 3-Acetyl-7-Oxo-Dehydroepiandrosterone (7-Keto™DHEA) if it is found to be unsafe, adulterated or misbranded. It is the responsibility of the manufacturer or distributor of a dietary supplement to ensure that it is safe, properly labeled and complies with all applicable requirements of the Federal Food, Drug and Cosmetic Act and implementing regulations in Title 21 of the Code of Federal Regulations as well as any other applicable Federal laws and regulations. Importantly, any new dietary ingredient for use in a dietary supplement that FDA has reviewed through the premarket notification process is not "approved" or "authorized" by the agency.

Your notification will be kept confidential for 90 days from the date of the effective filing date. Therefore, after October 27, 2002, your notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public. Prior to the 90-day period, you may wish to identify in writing specifically what information you believe is proprietary in your current notification for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

For your information, the following FDA Internet sites and their corresponding links may be useful:
http://www.cfsan.fda.gov/~dms/supplmnt.html
http://www.cfsan.fda.gov/~lrd/fr97923e.html (21 CFR 190.6)
http://www.cfsan.fda.gov/~dms/ds-info.html
http://www.cfsan.fda.gov/~dms/ds-ind.html
http://www.cfsan.fda.gov/~dms/ds-labl.html
http://www.cfsan.fda.gov/~lrd/fr97923b.html
http://www.cfsan.fda.gov/~dms/ds-labl.html#structure
http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm

Please contact me at (301) 436-2371, if you have any questions concerning this matter.

Sincerely yours,

Gloria Chang

Gloria Chang, R.Ph
Interdisciplinary Scientist
HFS-821
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Regulatory Affairs
502 Eastern Avenue, Plt. 6
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Fax: 616-673-9078
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Perrigo Company

Fax

To: Gloria Chang **From:** David Jespersen

COMPANY: FDA **COMPANY:** Perrigo

Fax: (301) 436-2636 **Date:** 9/13/02

Phone: (301) 436-1853 **Phone:** (616) 673-7595

Pages: (Incl. Cover)

Re: Perrigo Company July 25 7-Keto **CC:**

☑ **Urgent** ☐ **For Review** ☐ **Please Reply**

•Comments:

Attached is a copy of the reference that you requested on September 13th. While this is a 11 page report it would seem that you would have adequate time to review this and the rest of the Filing within the original 75 day clock. If you have any Further questions, please feel Free to contact me. Sincerely David Jespersen

Document (11 pages) was removed in its entirety because it contained confidential commercial trade information.

PERRIGO®

July 25, 2002

Division of Standards and Labeling Regulations
Office of Special Nutritionals(HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Dear Sir or Madam:

Perrigo Company is notifying the Food and Drug Administration that it will market 7-Keto™. Following Section 413 (350b) of the Federal Food, Drug and Cosmetic Act and Title 21 of the Code of Federal Regulations 190.6 please find two copies of this notification.

Trade name of the compound 7-Keto™ DHEA, labeling 3-Acetyl-7-Oxo-Dehydroepiandrosterone, chemical name: 3β-Acetoxyandrost-5-en-7, 17-dione and the CAS number: 1449-61-2.

The dietary supplement will contain 100 mg 3-Acetyl-7-Oxo-Dehydroepiandrosterone per tablet. Suggested use will be for adults up to two times per day.

In the attached is the basis for safe use. This summary utilized published and unpublished research establishing reasonable safe use of this new dietary ingredient under recommended conditions.
Including:

1. Safety profile.

2. Covance Laboratories, Inc.. Summary from Mutagenicity test with HD-9001, 3-acetyl-7-oxo-DHEA in the Salmonella–Escherichia coli/Mammilian–Microsome Reverse Mutation Assay.

3. Humanetics Corporation. Abstract for Safety and Pharmacokinetic Study of Oral HD-9001, 3-acetyl-7-oxo-DHEA Healthy Volunteers.

4. General Nutrition Corporation/Humanetics Corporation 7-Keto DHEA 75-day premarket notification.

81345

B2S.

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Confidential commercial reports 2 and 3 will be made available upon your request.

Sincerely,

Dave Jespersen
Director of Technical Services

CC: John Dykstra
Chief Operating Officer
Humanetics Corporation

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[redacted]

PERRIGO®

7-Keto Acetate

7-Keto is reasonably considered safe under the conditions recommended in labeling.

History and Use

Lieberman et al (1948) discovered but did not completely identify this β-ketosteroid in the urine of healthy and diseased individuals.

Fukushima et al (1954) found 3β-Hydro-Δ^5-androstene-7, 17-dione, (3β-acetyl-7-oxo-DHEA) in urine analyzed from normal and abnormal subjects. Subjects excreted 3β-acetyl-7-oxo-DHEA in larger amounts in adrenal abnormalities such as those with an increase in DHEA excretion.

General Nutrition Corporation has been marketing 7-Keto™ since 1998 and no adverse events have been reported on the Food and Drug Administrations Adverse Event Reporting web site.

Safety

One Safety assessments is a Mammilian-microsome reverse mutation study using 3β-acetyl-7-oxo-DHEA and/or its metabolites in *Salmonella-Escherichia coli.* This evaluated the ability to induce reverse mutations at the histidine locus in the genome specific *Salmonella typhiurium* tester strain and at the tryptophan locus in an *Escherichia coli* tester strain both in the presence and absence of exogenous metabolic activation system of mammalian microsomal enzyme (S9). In the presence and absence of S9 at doses of 0.1 to 5.0 mg per plate 3β-acetyl-7-oxo-DHEA did not cause an increase in the number of revertants per plant

Dosing considerations were based on the safety trial by Davidson et al clinical trial by Kalman et al and animal studies. Davidson et al (2000) reported serum levels of dihydrotestosterone, estradiol, cortisol and insulin were not affected by 7-Keto DHEA (3β-acetyl-7-oxo-DHEA) when compared to baseline levels after the escalating dose study of 50 mg/d 7days, 100 mg/d 7 days, 200 mg/d 28 days). Thyroxin and total testosterone were both noted with a decreases ($p<0.05$ and $p<0.01$) but were within normal range. No statistical differences in clinical chemistries, urinalysis and hematology profiles were found between the 7-Keto DHEA and placebo group. No detrimental effects on vital signs or body weight were found for the 7-Keto DHEA group. Adverse events were not different between the 7-Keto DHEA group and the placebo group. The steroid 3β-acetyl-7-oxo-DHEA was rapidly converted to 7-oxo-DHEA-S proportionally to the does. Typical clearance and volume distribution was 172 L/h and 540 L.

In a clinical trial by Kalman et al (2000) 7-Keto DHEA 100mg was taken twice a day (200mg/d) for eight weeks. T3 increased slightly, not out of normal range, and there were

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no changes in TSH or T4. No significant changes were observed in blood sugar levels, testosterone, estradiol, liver, renal function tests or vital signs.

In a study by Zenk et al (unpublished) no serious side effects were reported with 200 mg per day of 3-acetyl-7-oxo-DHEA for four weeks.

Acute oral gavage toxicity study (Lardy et al, 1999) of rats found a 2000 mg/kg no-observable-adverse-effect-level for a single does. No differences were found in body weight, and there were no apparent effects on the anatomical pathology results in a dosing range of 250-1000 mg/kg. All animals survived until scheduled sacrifice.

Escalating dose oral gavage toxicity study in Rhesus monkeys (Henwood et al 1999) found that 1000 mg/kg/day for 5 consecutive days had no apparent adverse effect on clinical or anatomical pathology. No notable effects on body weight for the dosing range of 250 to 1000 mg/kg/day. All animals survived until scheduled sacrifice.

From the data available it was determined 100 mg up to twice daily would be well-tolerated in humans.

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Safety and Pharmacokinetic Study of Oral 7-Keto DHEA in Healthy Volunteers

Humanetics, Inc.

ABSTRACT

This report describes the results of pharmacokinetic analysis of a study performed to obtain safety information on 3 acetyl-7-oxo-DHEA following oral administration at 3 dosage levels, to obtain pharmacokinetic data on 3 acetyl-7-oxo-DHEA, and to relate plasma 3 acetyl-7-oxo-DHEA levels to dosage level in healthy adults.

Twenty-two healthy adult male volunteers completed the study. Subjects were randomized to receive either 3 acetyl-7-oxo-DHEA (N=16) or placebo (N=6). Three doses levels were tested in an escalating dose design. A b.i.d. regimen was utilized, as follows. The first dosage level of 50 milligrams daily was composed of 25 mg b.i.d. The second dosage level (100 mg daily) was 50 milligrams b.i.d.. The final regimen (200 mg daily) consisted of 100 milligrams b.i.d.

At the first dosage level of 50 milligrams per day, subjects took their medication (active compound or placebo) twice daily 12 hours apart for a seven-day period. Subjects then underwent safety assessment before proceeding with dosing at the next higher level. Blood was obtained at 12 hours following the last evening's 25-milligrams dose to assess trough levels of the parent compound and/or its metabolites. The second dosage level of 100 milligrams per day continued similarly for a seven-day period. followed by safety assessment before proceeding with dosing at the next higher level. The third and final dosage level of 200 milligrams daily (active compound or placebo) continued for a four-week period. After completing seven days of dosing at this level, subjects returned to the clinic for safety assessment before continuing with dosing at this level for the remainder of the four-week period.

At the end of the four-week period of dosing at the two hundred milligram level, all of the subjects who had participated in the escalating dose study participated in the pharmacokinetic study. Twelve hours after taking the last evening dose, subjects received a single dose of one hundred milligrams of 3 acetyl-7-oxo-DHEA and blood samples were drawn by venipuncture at 0, 0.25, 0.5, 1, 2, 4, 6, and 12 hr following dosing for measurement of plasma levels of parent compound and/or metabolites.

An analytical method was developed for quantitation of 7-oxo-DHEA-3-sulphate in human plasma. This was an HPLC method which utilized calibration curves for 7-oxo-DHEA-3-sulphate in the range of 10 to 500 ng/ml.

Predose (trough) plasma concentrations of 7-oxo-DHEA-3-sulphate during the escalating dose study in the placebo-treated group (N=6) were close to the limit of quantitation. Trough plasma levels in the subjects receiving active compound (N=16) were proportional to daily dose, supporting the use of a linear pharmacokinetic model in the

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analysis of the data. Mean pre-dose levels in subjects in the active compound group at the 200 mg/day level measured after approximately 4 weeks of dosing (16.3 mcg/L) were

similar to those determined after 1 week of dosing (15.8 mcg/L) suggesting that the ratio of the formation rate of this metabolite to its elimination clearance is constant during multiple dosing.

Pharmacokinetic analysis of the plasma concentrations of the metabolite of HL-9001, i.e., 7-oxo-DHEA-3-sulphate, was performed for the pharmacokinetic study as follows. Cmax and Tmax values for the metabolite were determined by inspection. The mean time to peak plasma level (Tmax) was 2.2 hr, reflecting rapid absorption of the parent compound and conversion to the 7-oxo-DHEA-3-sulphate metabolite. The mean Cmax for
7-oxo-DHEA-3-sulphate metabolite. The mean Cmax for 7-oxo-DHEA-3-sulphate was 158 mcg/L.

Noncompartmental analysis if the plasma concentration-time data for the metabolite, 7-oxo-DHEA-3-sulphate, involved determination of the area under the plasma concentration-time curve using the linear trapezoidal rule to the last sampling time, and, where the terminal elimination half-life could be estimated, to time infinity. The terminal elimination half-life (T1/2) of 7-oxo-DHEA-3-sulphate was determined by regression analysis of the log plasma concentration-time curves. The average half-life (harmonic mean) for 7-oxo-DHEA-3-sulphate was determined by regression analysis of the log plasma concentration-time curves. The average half-life (harmonic mean) for 7-oxo-DHEA-3-sulphate was 2.17 hr.

The mean AUC to t last was 665 mcg-hr/L, and the mean AUC to inf was 724 mcg-hr/L. The ratio of AUC to t last relative to AUC inf averaged 96%, reflecting the short half-life in relation to the sampling period.

Apparent clearance of 7-oxo-DHEA-3-sulphate for subjects receiving active compound during the escalating dose study was calculated as the dose divided AUC to 12 hr, or as the dose divided by AUCinf for placebo subjects who were receiving their first dose of active HL-9001 as the pharmacokinetic test dose. The apparent clearance, CL/F, averaged 172 L/hr (N=22) No physiological interpretation on this parameter is possible, since the bioavailability of the parent compound and the fraction of its disposition which results in generation of the 7-oxo-DHEA-3-sulphate metabolite is unknown.

The apparent volume of distribution, V/F, of 7-oxo-DHEA-3-sulphate in the terminal elimination phase was similarly calculated for subjects receiving active compound or placebo from the AUC to 12 hr or AUCinf, respectively. The apparent volume of distribution (V/F) averaged 540 L.

Simulations of plasma concentrations of 7-oxo-DHEA-3-sulphate were performed to represent the regimens employed in the dose escalation study. Nine hypothetical subjects were used in the simulations, employing three levels of apparent clearance, and three levels of the apparent volume distribution, resulting in a 3x3 array. The typical subject

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exhibited apparent clearance and volume of distribution of 172 L/hr and 540 L, respectively. A one-compartment model was assumed with first-order absorption and no

lag phase. It was assumed that conversion of parent compound to the 7-oxo-DHEA-3-sulphate metabolite was so rapid that the metabolite profile followed closely that of the parent compound, i.e., that it was biexponential.

The dosing regimens in the simulations were identical to those employed in the escalating dose study. Thus, subjects received 25 milligrams b.i.d., followed by a washout period. Subsequently, the dose of HL-9001 was 50 milligrams b.i.d., again followed by a washout period. Finally, a regimen of 100 milligrams b.i.d. was simulated. There was good agreement between simulated and measured means of the trough plasma levels. Plasma concentrations of 7-oxo-DHEA-3-sulphate were also simulated over one dosing interval following a 100-mg dose of HL-9001 using the same parameters. Agreement between mean measured and simulated plasma concentrations of 7-oxo-DHEA-3-sulphate over a dosing interval was reasonable.

Date of Report
April 27, 1998

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Reference:

Davidson M, Marwah A, Sawchuck RJ, Maki K, Marwah P, Weeks C and Lardy H. *Safety and pharmacokinetic study with escalating doses of 3-acetyl-7-oxo-dehydroepiandrosterone in healthy male volunteers.* Clin Invest Med. 2000; 23(5):300-310.

Fukushima DK, Kemp AD, Schneider R, Stokem MB and Gallagher TF. *Studies in steroid Metabolism XXV. Isolation and characterization of New Urinary Steroids.* J of Bio Chem. 1954; 210:129-137.

Henwood SM, Weeks CE and Lardy H. *An Escalating dose oral gavage study 3beta-acetoxyadrost-5-ene-7,17-dione (7-oxo-DHEA-acetate) in rhesus monkeys.* Biochem Biophys Res Commun. 1999; 254(1):124-126.

Kalman DS, Colker CM, Swain Ma, Torina GC and Shi Q. *A Randomized, Double-Blind, Placebo-Controlled Study of 3-Acetyl-7-Oxo-Dehydroepiandrsterone in Healthy Overweight Adults.* Current Therapeutic Res. 2000; 61(7):435-442.

Lardy H, Henwood SM and Weeks CE. *An Acute oral gavage study of 3beta-acetoxyadrost-5-ene-7,17-dione (7-oxo-DHEA-acetate) in rats.* Biochem Biophys Res Commun. 1999; 254(1):120-123.

Lieberman S, Dobriner K, Hills BR, Fieser LF and Rhoads CP. *Studies in Steroid Metabolism II. Identification and Characterization of Ketosteroids Isolated From Urine of Healthy and Diseased Persons.* J of Bio Chem. 1948; 172:263-295.

Sunde A, Aareskjold K, Haug E and Eil-Nes KB. *Synthesis and Androgen Effects of 7α,17β-Dihydroxy-5α-Androstan-3-One, 5α-Androstan-3α,7α,17β-Triol and 5α-Androstane-3β,7α,17β-Triol.* J Steroid BioChem. 1982; 16:483-488.

Zenk JL. *The Use of 3-Acetyl-7-Oxo-Dehydroepiandrosterone for Augmenting Immune Response in the Elderly.* Unpublished.

General Nutrition Corporation 75-day premarket notification.

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