

**The Conseco Brand Sea Buckthorn Fruit Oil
Towards
Pre-market Notification for Dietary Supplement Substance in USA**

Han Xu, M.D.
Conseco Sea buckthorn Co., Ltd.
Jia 1 Fuxing Road, Haidian District, Beijing 100038, P. R. China.
Tel: 0086-010-63205022, Fax: 0086-010-63204359
E-mail: infor@pharm1.com or hanxu62@sina.com

Susan Walker, M.D.,
Division Director,
Division of Dietary Supplements Programs,
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820),
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway, College Park, MD 20740
Telephone number: 301 436 - 2375

α.B/FOA

Dear FDA Officer Dr. Susan Walker - Director,

**Subject: Conseco Brand Sea Buckthorn Fruit Oil towards 75-Day Pre-market Notification
for Dietary Supplement Substance in USA (Re-submission)**

Thank you for your informing letter on November 19, 2003.

We re-submit the new documents about "Conseco Brand Sea Buckthorn Fruit Oil towards 75-Day Pre-market Notification for Dietary Supplement Substance in USA" to FDA CFSAN. We had submitted the similar documents about the Conseco Brand Sea Buckthorn Fruit Oil to FDA CFSAN on September 4, 2003 and received FDA CFSAN informing letter on November 19, 2003. Base on your viewpoints in the informing letter, we organize our documents newly. Please arrange relevant Officers to review the documents according to "Federal Food, Drug, and Cosmetic Act" of USA again, in order to let us finish the whole notification process of the product.

Thank you for again.

We are looking forward to hearing from you as soon as possible.

Best wishes,
Sincerely yours,

Han Xu
Han Xu, M.D.
Senior Researcher

Conseco Sea buckthorn Co., Ltd.
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All of materials I will send an original and two copies (3 copies).

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

My name and complete address:

Han Xu, M.D.
Conseco Sea buckthorn Co., Ltd.
Jia 1 Fuxing Road, Haidian District, Beijing 100038, P. R. China.
Tel: 0086-010-63205022, Fax: 0086-010-63204359
E-mail: infor@pharm1.com or hanxu62@sina.com

The name of the new dietary ingredient:

The Conseco Brand Sea Buckthorn Fruit Oil

The description of the dietary ingredient substance:

This is the 100% natural herbal dietary supplement substance obtained from the botanical fruits of Sea buckthorn (*Hippophae rhamnoides* L.).

Through processed as following: select the rape fruits of Sea buckthorn (*Hippophae rhamnoides* L.), clean the fruits with water, squeeze the fruits to produce liquid-like matters, centrifuge the matters and fine works to produce The Conseco Brand Sea Buckthorn Fruit Oil.

Like as the material substance of dietary supplement, we recommend that the product can be used into the **Specification:** 100ml/bottle of The Conseco Brand Sea Buckthorn Fruit Oil about the **Dosage:** 20ml per day (5~10ml/time, 2 times/day, oral administration).

Note: The Conseco Brand Sea Buckthorn Fruit Oil is 100% herbal Sea Buckthorn Fruit Oil extract. Like as dietary ingredient material substance, distribute towards manufacturers or through distributors, not towards retailers.

Our products abide by following P. R. China Industry Standards:

Sea buckthorn Fruit Oil
The Industry Standards of P. R. China
HB/QS 001—94
1994—06—08 Published
1994—10—17 Implemented
Published by National Sea buckthorn Coordination Office
[Detailed in Document Digest (P-1)]

Conseco Sea buckthorn Co., Ltd.
Jia 1 Fuxing Road, Haidian District, Beijing 100038, P. R. China.
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Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Green Trade Standards of Importing & Exporting Medicinal Plants & Preparations
P. R. China Foreign Trade Industry Standards
WM2-2001

Ministry of Foreign Trade and Economic Cooperation, PRC
(Ministry of Commerce P. R. China)

2001—04—23 Published

2001—07—01 Implemented

[Detailed in Document Digest (T)]

The level of the dietary ingredients in the product:

Dietary Ingredients: 100% The Conseco Brand Sea Buckthorn Fruit Oil
(100% herbal Sea Buckthorn Fruit Oil extract)
Total Carotenoid (mg/100g) , ≥ 150
 β - carotene (mg/100g) , ≥ 5
Vitamin E (mg/100g) , ≥ 100 .
 α - tocopherol (mg/100g) , ≥ 60 .

The conditions of use of the product:

Like as the botanical material substance of dietary supplement, we recommend that the product can be used into the **Specification:** 100ml/bottle of The Conseco Brand Sea Buckthorn Fruit Oil about the **Dosage:** 20ml per day (5~10ml/time, 2 times/day, oral administration).

The label contents of the product:

Brand Name: Conseco Brand.

Product Name: Sea Buckthorn Fruit Oil.

Serving Size: 100ml/bottle, or according to client requirements.

Dietary Ingredients: 100% The Conseco Brand Sea Buckthorn Fruit Oil
(100% herbal Sea Buckthorn Fruit Oil extract)
Total Carotenoid (mg/100g) , ≥ 150 .
 β - carotene (mg/100g) , ≥ 5 .
Vitamin E (mg/100g) , ≥ 100 .
 α - tocopherol (mg/100g) , ≥ 60 .

Recommendation: Like as the botanical material substance of dietary supplement, we recommend that the product can be used into the **Specification:** 100ml/bottle of The Conseco Brand Sea Buckthorn Fruit Oil about the **Dosage:** 20ml per day (5~10ml/time, 2 times/day, oral administration).

Claim: This is the 100% natural herbal dietary supplement. The statement has not been evaluated or approved by the FDA of USA. The product is not intended to diagnosis, treat, cure, or prevent any disease.

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Alert: Keep out the children. Forbid in diarrhea.

Store: Store at a cool & dry location.

Distributor: Conseco Sea buckthorn Co., Ltd.

Jia 1 Fuxing Road, Haidian District, Beijing 100038, P. R. China.

Tel: 0086-010-63205022, Fax: 0086-010-63204359

E-mail: infor@pharm1.com or hanxu62@sina.com

The history of use like as herbal extraction in P. R. China:

According to the P. R. China Industry Standards as following:

Sea buckthorn Fruit Oil

The Industry Standards of P. R. China

HB/QS 001—94

1994—06—08 Published

1994—10—17 Implemented

Published by National Sea buckthorn Coordination Office

The history of the product used as herbal extraction in P. R. China should be beginning in 1994-10-17 officially.

The other evidences of safety tests:

The recommended human usage for The Conseco Brand Sea Buckthorn Fruit Oil is 20ml oral administration per day on our product label. This dosage does not present any safety concerns. According to 7-days acute toxic test in SD white rats, the results determine that the product LD50 is 40ml/kgbw. The maximum tolerance dosage (50ml/kg/day) in the 7-days test with SD white rats arrive 150 folds about the human usage (20ml/60kg/day) in the data record with Conseco Sea buckthorn Co., Ltd.. The Conseco Brand Sea Buckthorn Fruit Oil belongs to **non-toxicity grade in fact** according to the acute toxicity grade standards. In the 90-days long-term toxic experiment in SD rats, the experimental group rats (group 2, group 3, group 4) received The Conseco Brand Sea Buckthorn Fruit Oil dosages in the test with SD white rats, 2ml/Kg.BW, 5ml/Kg.BW, and 10ml/Kg.BW per day respectively arrive 6, 15, and 30 folds about the human usage (20ml/60kg/day) in the data record with Conseco Sea buckthorn Co., Ltd.. Towards our recommended human usage for The Conseco Brand Sea Buckthorn Fruit Oil on our labeling, 20ml oral administration per day, the safety is enough.

7-days acute toxic test towards SD rats:

Test materials:

Conseco Sea buckthorn Co., Ltd.

Jia 1 Fuxing Road, Haidian District, Beijing 100038, P. R. China.

Tel: 0086-010-63205022, Fax: 0086-010-63204359

E-mail: infor@pharm1.com or hanxu62@sina.com

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Sample: The Conseco Brand Sea Buckthorn Fruit Oil. Brown red transparence uniformity oil state liquid. **Specification:** 100ml/bottle. **Distributor:** Conseco Sea buckthorn Co., Ltd.. **Quality Standard:** HB/QS 001-94.

Experiment Animals: healthy SD white rats, body weight 140~160g. Supplied by Laboratory Animals Center, NATIONAL INSTITUTE FOR THE CONTROL OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS, PRC.

Methods:

The 50 healthy SD rats, 25 male and 25 female, divided into 5 groups random, half male and half female each group. After fasting 15 hours, Group 1, Group 2, Group 3 and Group 4 are dosage groups, respectively Injection Gastric (i.g.) 10ml/kg, 20ml/kg, 30ml/kg, 40ml/kg with The Conseco Brand Sea Buckthorn Fruit Oil, (2 times per day, interval 6 hours); Group 5 is control group, Injection Gastric (i.g.) with water. After usage like as above, divide cages and foster crowds with same conditions, solid feedstuff and normal drink. Observe 7 days at room temperature (20°C -25°C) continuously, and record animal death and general instances, including body weight, breath, heart rhythm, reflect, spirit, behavior, appearance, etc.

Results:

The observation results show that, there is no animal death in all of 5 groups in the test term. At the day 1, the rats with The Conseco Brand Sea Buckthorn Fruit Oil present with activity and appetite decrease, appear oiliness dejecta, contaminate hairs with oiliness around anus; day 2 - day 3, appetite, defecation, and activity recover gradually; the other observation indexes, such as diet, behavior, spirit, breath, there is no significant difference comparison with control group. So the report determines that the product LD50 is 40ml/kgbw according to above test.

Conclusion:

The test results towards The Conseco Brand Sea Buckthorn Fruit Oil show that: according to the 7-days acute toxic tests in SD rats, the report determines that the product LD50 is 40ml/kgbw and belongs to **non-toxicity grade in fact** according to the acute toxicity grade standards.

The maximum tolerance dosage assay:

Test materials:

Sample: The Conseco Brand Sea Buckthorn Fruit Oil. Brown red transparence uniformity oil state liquid. **Specification:** 100ml/bottle. **Distributor:** Conseco Sea buckthorn Co., Ltd.. **Quality Standard:** HB/QS 001-94.

Experiment Animals: healthy SD white rats, body weight 140~160g. Supplied by Laboratory Animals Center, NATIONAL INSTITUTE FOR THE CONTROL OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS, PRC.

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Methods:

The 40 healthy SD rats, 20 male and 20 female, divided into 2 groups random, half male and half female each group. After fasting 15 hours, Group 1 is dosage group, the rats Injection Gastric (i.g.) 50ml/kg with The Conseco Brand Sea Buckthorn Fruit Oil, (2 times per day, interval 6 hours); Group 2 is control group, Injection Gastric (i.g.) with water. After usage like as above, divide cages and foster crowds with same conditions, solid feedstuff and normal drink. Observe 7 days at room temperature (20°C-25°C) continuously, and record animal death and general instances, including body weight, breath, heart rhythm, reflect, spirit, behavior, appearance, etc.

Results:

The observation results show that, there is no animal death in all of 2 groups in the test term. At the day 1, the rats with The Conseco Brand Sea Buckthorn Fruit Oil present with activity and appetite decrease, appear oiliness dejecta, contaminate hairs with oiliness around anus; day 2 - day 3, appetite, defecation, and activity recover gradually; the other observation indexes, such as diet, behavior, spirit, breath, there is no significant difference comparison with control group. Until day 8, end experiment, do autopsy to observe thoracic and abdominal cavity, the results show that there is no significant difference comparison to control group; there are no macroscopic pathological changes in heart, liver, spleen, lung, kidney and stomach & intestine in all 2 groups of mice.

Conclusion:

According to above experimental conditions, each dosage group SD rat Injection Gastric (i.g.) 50ml/kg with The Conseco Brand Sea Buckthorn Fruit Oil, (2 times per day, interval 6 hours), observe 7 days, there is no obvious toxic reaction towards The Conseco Brand Sea Buckthorn Fruit Oil in the SD rats. The results show that the ingredient substance SD rat i.g. LD50 > 50ml/kg in the maximum tolerance dosage assay.

According to human usage data recorded by Conseco Sea buckthorn Co., Ltd., adult human can take 20ml per day (5~10ml/time, 2 times/day) oral administration with The Conseco Brand Sea Buckthorn Fruit Oil, count the average adult human body weight like as 60kg in P. R. China, we can get the results as following:

$$\frac{\text{The maximum tolerance dosage in the test (50ml/kg/day)}}{\text{The human usage in the data record (20ml/60kg/day)}} = 150 \text{ folds}$$

Therefore, the maximum tolerance dosage (50ml/kg/day) in the test with SD white rats arrive 150 folds about the human usage (20ml/60kg/day) in the data record with Conseco Sea buckthorn Co., Ltd.. The Conseco Brand Sea Buckthorn Fruit Oil belongs to **non-toxicity grade in fact** according to the acute toxicity grade standards.

90-days long-term toxic experiment in SD rats:

Test materials:

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Sample: The Conseco Brand Sea Buckthorn Fruit Oil. Brown red transparency uniformity oil state liquid. **Specification:** 100ml/bottle. **Distributor:** Conseco Sea buckthorn Co., Ltd.. **Quality Standard:** HB/QS 001-94.

Experiment Animals: healthy SD white rats, body weight 100~120g. Supplied by Laboratory Animals Center, NATIONAL INSTITUTE FOR THE CONTROL OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS, PRC.

Methods:

In the 90-days long-term toxic experiment in SD rats, SD species of weight 100-120g, half male, half female, total 80 SD rats. After feed one week in laboratory conditions and be divided four groups random according to body weight and sex, the 80 SD rats are divided into three groups (group 2, group 3, group 4) for experiment and another group for control (group 1); each group contains 20 rats, half male, half female. The control group rats (group 1) received water 10ml/Kg.BW, and the experimental group rats (group 2, group 3, group 4) received The Conseco Brand Sea Buckthorn Fruit Oil 2ml/Kg.BW, 5ml/Kg.BW, and 10ml/Kg.BW, [one time per day, with ig (injection gastric) each time] and continue to feed each rat for 3 months. Divide cages and foster crowds with same conditions, solid feedstuff and normal drink. The rats are measured body weight per 10 days, and observed activity, appetite, dejecta, and hair color.

Results:

The observation results show that, there is no animal death in all of 4 groups in the test term. After observing for 3 months, there is no significant difference comparison by control group ($p>0.05$) in body weight (BW), and there is no death. About hair color and behavior change in the three groups, there is no significant difference comparison by control group, except some high dose group rats have soft dejecta, light yellow hair, and a little appetite decrease. Also they do the blood tests, including HB, RBC, and WBC indexes, all the blood tests are in the normal range. There is no significant difference comparison by control group SD rats ($P>0.05$). As well as they do other blood biochemistry index tests, including SGPT, SGOT, BUN, creatinine and blood sugar, all test results are in the normal range, and there is no significant difference comparison to control group SD rats ($P>0.05$). There are no macroscopic pathological changes in the heart, liver, spleen, kidney, adrenal gland, testis, womb & oval gland, and thymus gland, all organ weights are in the normal ranges, there is no significant difference comparison to control group SD rats ($P>0.05$).

Conclusion:

The experimental group rats (group 2, group 3, group 4) received The Conseco Brand Sea Buckthorn Fruit Oil 2ml/Kg.BW, 5ml/Kg.BW, and 10ml/Kg.BW per day respectively. According to human usage data recorded by Conseco Sea buckthorn Co., Ltd., adult human can take 20ml per day (5~10ml/time, 2 times/day) oral administration with The Conseco Brand Sea Buckthorn Fruit Oil, count the average adult human body weight like as 60kg in P. R. China, we can get the results as following:

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

$$\frac{\text{The dosage group 2 in the test (2ml/kg/day)}}{\text{The human usage in the data record (20ml/60kg/day)}} = 6 \text{ folds}$$

$$\frac{\text{The dosage group 3 in the test (5ml/kg/day)}}{\text{The human usage in the data record (20ml/60kg/day)}} = 15 \text{ folds}$$

$$\frac{\text{The dosage group 4 in the test (10ml/kg/day)}}{\text{The human usage in the data record (20ml/60kg/day)}} = 30 \text{ folds}$$

Therefore, the experimental group rats (group 2, group 3, group 4) received The Conseco Brand Sea Buckthorn Fruit Oil dosages in the test with SD white rats, 2ml/Kg.BW, 5ml/Kg.BW, and 10ml/Kg.BW per day respectively arrive 6, 15, and 30 folds about the human usage (20ml/60kg/day) in the data record with Conseco Sea buckthorn Co., Ltd.. Towards our recommended human usage for The Conseco Brand Sea Buckthorn Fruit Oil on our labeling, 20ml oral administration per day, the safety is enough.

Other adverse substances assay:

Document Digest

China National Analysis And Test Center For Sea Buckthorn Product

CERTIFICATE OF ASSAY

Product Batch Number: 20030417.

Department of Delivery: Conseco Sea buckthorn Co., Ltd.

Department of Distributor: Conseco Sea buckthorn Co., Ltd.

Name of Sample: The Conseco Brand Sea Buckthorn Fruit Oil

Specification: 100ml/bottle.

Quantity of Sample: 500ml/5bottles.

Quality Standard: WM2-2001.

(This is just certificated for the delivered sample)

The Conseco Brand Sea Buckthorn Fruit Oil is distributed by Conseco Sea buckthorn Co., Ltd.. They sent the samples of The Conseco Brand Sea Buckthorn Fruit Oil (**Product Batch Number:** 20030417) for analysis, and they received the data from the China National Analysis And Test Center For Sea Buckthorn Product. The following data measured per bottle are listed below.

Average concentration amount of impurities, toxins and pesticides in one of bottle of the The Conseco Brand Sea Buckthorn Fruit Oil:

Overview - The Conseco Brand Sea Buckthorn Fruit Oil

Heavy Metal and Arsenate:

Total Heavy Metal <20.0 mg/kg

Pb <5.0 mg/kg

Cd <0.3 mg/kg

Hg <0.2 mg/kg

Cu <20.0 mg/kg

As <2.0 mg/kg

Aflatoxin Content:

B1(Aflatoxin) <5 μg/kg

Pesticide Residual Quantity

BHC <0.1 mg/kg

DDT <0.1 mg/kg

PCNB <0.1 mg/kg

Aldrin <0.02 mg/kg

Microbiology Indexes:

Escherichia coli -- 0/ml

Staphylococcus aureus -- 0/ml

Pseudomonas aeruginosa -- 0/ml

The amount of impurities and toxins measured are lower than that specified in the P. R. China food standard.

My signature by myself you can contact me if you have any questions



Han Xu, M.D.

Conseco Sea buckthorn Co., Ltd.

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All of text materials I will send an original and two copies (3 copies).

Attachments

--- Document Digest (P-1) ---

Sea buckthorn Fruit Oil
 The Industry Standards of P. R. China
 HB/QS 001—94
 1994—06—08 Published
 1994—10—17 Implemented
 Published by National Sea buckthorn Coordination Office

Table 1 Appearance Indexes

Item	Index
	Sea buckthorn Fruit Oil
Description	Brown red transparence uniformity oil state liquid, viscid under low temperature.
Odor & Taste	Contain Sea buckthorn Fruit Oil inherent flavour and taste, no offodour.

Table 2 Indexes of Physics And Chemistry

Item	Index
	Sea buckthorn Fruit Oil
Density (20°C)	0.9100—0.9400
Refractive Index (20°C)	1.4500—1.4800
Acid value (mg KOH/g), ≤	40
Iodin value (g/100g)	18—70
Saponification value (mg KOH/g)	130—200
Nonsaponification (%) ≥	1
Total Carotenoid (mg/100g), ≥	150
β - carotene (mg/100g), ≥	5
Vitamin E (mg/100g), ≥	100
α - tocopherol (mg/100g), ≥	60
Character Value (C60, %), ≥	25
Moisture (%), <	0.3

Table 3 Hygiene Indexes

Item	Index
Peroxy Value (ex factory, %), ≤	0.40
As (ppm), ≤	0.1
Hg (ppm), ≤	0.05
Residue Solvent (ppm)	0

Attachments

--- Document Digest (T) ---

Green Trade Standards of Importing & Exporting Medicinal Plants & Preparations

P. R. China Foreign Trade Industry Standards

WM2-2001

Ministry of Foreign Trade and Economic Cooperation, PRC

(Ministry of Commerce P. R. China)

2001-04-23 Published

2001-07-01 Implemented

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4. Limited Quantity Indexes

4. 1. Heavy Metal and Arsenate

4. 1. 1. Total Heavy Metal ≤ 20.0 mg/kg

4. 1. 2. Pb ≤ 5.0 mg/kg

4. 1. 3. Cd ≤ 0.3 mg/kg

4. 1. 4. Hg ≤ 0.2 mg/kg

4. 1. 5. Cu ≤ 20.0 mg/kg

4. 1. 6. As ≤ 2.0 mg/kg

4. 2. Aflatoxin Content

4. 2. 1. B1(Aflatoxin) ≤ 5 μ g/kg

4. 3. Pesticide Residual Quantity

4. 3. 1. BHC ≤ 0.1 mg/kg

4. 3. 2. DDT ≤ 0.1 mg/kg

4. 3. 3. PCNB ≤ 0.1 mg/kg

4. 3. 4. Aldrin ≤ 0.02 mg/kg

4. 4. Microbiology Indexes: Escherichia coli -- 0/g or 0/ml

Staphylococcus aureus -- 0/g or 0/ml

Pseudomonas aeruginosa -- 0/g or 0/ml

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