

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

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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

P.B. FDA

Dear FDA Officer Dr. Susan Walker - Acting Director,

**Subject: Conseco Brand Sea Buckthorn Granule towards 75-Day Pre-market Notification
for Dietary Supplement Substance in USA**

Thank you for your reading.

We are Conseco Sea buckthorn Co., Ltd.. Right now, we submit the documents about "Conseco Brand Sea Buckthorn Granule towards 75-Day Pre-market Notification for Dietary Supplement Substance in USA" to FDA, CFSAN. Please relevant Officers review the documents according to "Federal Food, Drug, and Cosmetic Act" of USA, and tell us all of your viewpoints, in order to let us finish the whole notification process of the product.

Thank you for your considering.

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

Sincerely yours,

Han Xu

Han Xu, M.D.
Senior Researcher

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My signature by myself you can contact me if you have any questions..... 8

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

My name and complete address:

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The name of the new dietary supplement:

The Conseco Brand Sea Buckthorn Granule

The description of the dietary supplement substance:

This is the 100% natural herbal dietary supplement substance obtained from the botanical fruits of Sea buckthorn (*Hippophae rhamnoides* L.). The fresh ~~Sea Buckthorn fruit juice and fruit residue ethanol solutions~~ are concentrated and made into Granule with sugar. Like as the material substance of dietary supplement, we recommend that the product can be used as package in 15g/bag, oral administration (to be taken after being mixed with warm water) ,
[Specification: 15g/bag] [Dosage: 15g/time, 3 times/day]

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

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

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

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Overview - The Conseco Brand Sea Buckthorn Granule

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

The level of the dietary ingredients in the product:

Dietary Ingredients: Sea Buckthorn Fruit Extraction — 90g/100g
Sugar — 10g/100g
Vitamin C ≥ 0.2 g/100g
Total Flavones ≥ 0.13 g/100g

The conditions of use of the product:

Like as the botanical material substance of dietary supplement, we recommend that the product can be used as package in 15g/bag, oral administration (to be taken after being mixed with warm water) , [**Specification:** 15g/bag] [**Dosage:** 15g/time, 1 time/day]

The label contents of the product:

Brand Name: Conseco Brand.

Product Name: Sea Buckthorn Granule.

Serving Size: According to customer requirements.

Dietary Ingredients: Sea Buckthorn Fruit Extraction — 90g/100g
Sugar — 10g/100g
Vitamin C ≥ 0.2 g/100g
Total Flavones ≥ 0.13 g/100g

Recommendation: Like as the botanical material substance of dietary supplement, we recommend that the product can be used as package in 15g/bag, oral administration (to be taken after being mixed with warm water) , [**Specification:** 15g/bag] [**Dosage:** 15g/time, 1 time/day].

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 Granule

Alert: Keep out the children. Forbid in diabetes. Pay attention to body weight.

Store: Store at a cool & dry location.

Distributor: Conseco Sea buckthorn Co., Ltd.

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The evidences of safety tests:

The recommended human usage for Sea buckthorn Granule is 15g per day on our product label. This dosage does not present any safety concerns. According to 7-days acute toxic test and 60-days long-term test, the results cannot determine LD50 dosage in Kunming mice and Wistar rats actually. But the results can indicate that, in 7-days acute toxicity test towards Kunming mice, the maximum tolerance dose per day should be raw medicine 216g/kgBW, equal to 266.67 times of clinical usage (40.5g/day) (in P. R. China). So Sea Buckthorn Granule should have almost no toxicity. The dosages in the two experimental groups used in the 60-days long-term toxicity studies in Wistar rats, raw medicine 10g/kgBW (equivalent to 12.5 times clinical dosage) and raw medicine 20g/kgBW (equivalent to 25 times clinical dosage), ig (injection gastric), 1 time/day, continue 2 months. Except body weight of rats increase obviously, examine animal activity, peripheral blood indexes, liver & kidney function biochemistry indexes, and important organs pathology, there is no significant difference comparison to control group. So it should be safe to take the product long term.

About acute toxicity

An acute toxicity test of Sea Buckthorn Granule

Zhang Xiao¹, Su Mei-Ying², Zhang Tao³

1. Lanzhou Pharmaceutical Factory, Gansu Lanzhou 730046;
 2. Lanzhou Lung Hospital, Gansu Lanzhou 730046;
 3. Lanzhou Foci Pharmaceutical Factory, Gansu Lanzhou 730046;
- Hippophae 2001.06; 14(2): 38-39

Material Sample: Sea Buckthorn Granule, including raw medicine 0.9g/g.

Animals: Kunming species mice, closed animal community. Body Weight (BW) 18~22g, half male and half female. Supplied by Laboratory Animal Center, Lanzhou Biologic Product Institute of Ministry of Public Health.

Methods and Results:

According to the acute toxic test, the article cannot determine LD50 dosage in Kunming mice. But the article results can indicate that, in 7-days acute toxicity test towards Kunming mice, the maximum tolerance dose per day should be raw medicine 216g/kgBW, equal to 266.67 times of clinical usage. So Sea Buckthorn Granule has almost no toxicity.

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Overview - The Conseco Brand Sea Buckthorn Granule

- LD50 test:

The experiment results cannot determine LD50 dosage in Kunming mice.

- The test of the maximum tolerance dose per day:

20 healthy mice, half male and half female, use the maximum concentration of Sea Buckthorn Granule, raw medicine 1.8g/ml; according to usage 0.8ml/20gBW, ig (injection gastric); 3 times/day, total dosage/day should be raw medicine 4.32g/20gBW (raw medicine 216g/kgBW). Observe 7 days after medicine usage, there is no obvious abnormal reaction and no death in mice. The clinical dosage is 40.5g/day/person, and the average body weight is 50kg/person. The maximum tolerance dose in mice should be equal to 266.67 times of clinical usage.

Conclusion:

The experiment results cannot test LD50 dosage in Kunming mice. Use the maximum concentration, raw medicine 1.8g/ml; according to usage 0.8ml/20gBW, ig (injection gastric); 3 times/day, total dosage/day should be raw medicine 4.32g/20gBW (raw medicine 216g/kgBW). Observe 7 days after medicine usage, there is no toxic reaction and no death in mice. The maximum tolerance dose per day should be equal to 266.67 times of clinical usage. So the results demonstrate that Sea Buckthorn Granule has almost no toxicity.

About long-term toxicity

A long-term toxic experimental study of Sea Buckthorn Granule

Zhang Xiao¹, Su Mei-Ying², Zhang Tao³

1. Lanzhou Pharmaceutical Factory, Gansu Lanzhou 730046;
 2. Lanzhou Lung Hospital, Gansu Lanzhou 730046;
 3. Lanzhou Foci Pharmaceutical Factory, Gansu Lanzhou 730046;
- Hippophae 2001.12; 14(4): 20-22

Material Sample: Sea Buckthorn Granule, including raw medicine 0.9g/g.

Animals: Wistar rats, half male and half female, body weight (BW) 90~110g. Supplied by Laboratory Animal Center, Lanzhou Medical College.

Methods and Results:

The dosages in the two experimental groups used in the 60-days long-term toxicity studies, raw medicine 10g/kgBW (equivalent to 12.5 times clinical dosage) and raw medicine 20g/kgBW (equivalent to 25 times clinical dosage), ig (injection gastric), 1 time/day, continue 2 months. Except body weight of rats increase obviously, examine animal activity, peripheral blood indexes, liver & kidney function biochemistry indexes, and important organs pathology, there is no significant difference comparison to control group. So it is safe to take the product long term.

Overview - The Conseco Brand Sea Buckthorn Granule

- The experiment methods:

90 healthy rats are divided into three groups random, each group 30 rats, half male and half female, separately is fed for Sea Buckthorn Granule raw medicine 10g/kgBW, 20g/kgBW and normal saline (NS) equivalent volume (E.V.), ig (injection gastric), 1 time/day, continue 2 months. Every week regulate medicine usage according to animal body weight changes. The end of medicine usage period, after 24 hours, each group gets 20 rats random, examine peripheral blood indexes, serum biochemistry indexes, and important organs pathology (including macroscopic observation and tissue slide). After stopped medicine usage, the remainder rats in each group continue to be fed for 14 days normally, in order to observe reversibility of toxic reactions and deferment toxicities.

- The experiment results:

The general conditions:

In medicine usage period, observe rats' activities detailedly, and balance body weight of rats every week. In experiment, rats' activities are normal, and there is no significant difference in each group. After medicine usage 1 month and 2 month, the body weight of high dose and low dose group are increased separately, and there are significant differences comparisons to NS group. The results show in Table 1.

The peripheral blood indexes:

After the end of medicine usage, examine RBC counts, WBC counts, and WBC classify (DC). The results show that, in high dose and low dose group, there are no obvious changes about peripheral blood indexes, and there are no significant differences comparisons to NS group ($P > 0.05$). The results show in Table 2.

The serum biochemistry indexes:

After the end of medicine usage, get blood and keep blood static state 2 hours, 3000rpm centrifuge 10min, test BUN, Creatinine (Cr), SGPT, Icterus Index (I.I) (The results show in Table 3). Continuous medicine usage 2 months, about Sea Buckthorn Granule high and low dose group, examine liver & kidney function biochemistry indexes, there are no significant differences comparisons to NS group ($P > 0.05$).

The pathology examination:

Take important organs, including heart, liver, spleen, lung, and kidney, do macroscopic observation and tissue slide pathology, the results show that, there are no obvious pathological changes in Sea Buckthorn Granule high and low dose group.

The reversibility observation:

There is no abnormal reaction in reversibility observations about rest rats.

Overview - The Conseco Brand Sea Buckthorn Granule

Conclusion:

Sea Buckthorn Granule raw medicine 10g/kgBW (equivalent to 12.5 times clinical dosage) and raw medicine 20g/kgBW (equivalent to 25 times clinical dosage), ig (injection gastric), continue 2 months, the rats body weight of medicine usage groups are increased obviously, and there are significant differences comparisons to control group. About the rats' activities, peripheral blood indexes, liver & kidney functions, serum biochemistry indexes, and important organs pathology, there are no abnormal changes. The rest rats in each group continue to be observed 14 days after stopped medicine usage, and there is no abnormal reaction. The results indicate that it is safe to take Sea Buckthorn Granule long term.

Table 1 - The effects towards rat body weight about Sea Buckthorn Granule (n=30, A ± SD)

Group	Dosage (g/kg)	Body Weight Before Usage (g)	Body Weight After Usage (g)	
			1 month	2 months
NS	E.V.	98.4 ± 7.6	190.2 ± 10.8	236.4 ± 15.1
SB Granule	10	100.2 ± 7.7	205.8 ± 13.5*	289.5 ± 14.4*
SB Granule	20	98.1 ± 9.5	210.3 ± 13.8*	313.6 ± 22.1*

Note: group received Sea Buckthorn Granule comparison by NS group * P<0.05

Table 2 - The effects towards rat peripheral blood indexes about SB Granule (n=20, A ± SD)

Group	Dosage (g/kg)	RBC (10 ⁶ /mm ³)	WBC (10 ³ /mm ³)	DC (%)			
				neutrophilic granulocyte	eosinophil	lymphocyte	monocyte
NS	E.V.	7.40 ± 1.03	13.09 ± 3.41	14.37 ± 4.27	1.26 ± 0.21	79.82 ± 5.44	1.18 ± 0.27
SB Granule	10	7.12 ± 0.84	12.64 ± 3.20	14.72 ± 2.89	1.24 ± 0.25	80.18 ± 4.97	1.16 ± 0.29
SB Granule	20	7.45 ± 0.56	12.76 ± 4.33	14.94 ± 3.33	1.19 ± 0.27	78.75 ± 5.98	1.21 ± 0.32

Note: group received Sea Buckthorn Granule comparison by NS group P>0.05

Table 3 - The effects towards rat liver & kidney functions about SB Granule (n=20, A ± SD)

Group	Dosage (g/kg)	LI (μ/L)	SGPT (μ/L)	BUN (mmol/L)	Cr (mmol/L)
NS	E.V.	3.12 ± 0.39	35.52 ± 7.38	7.03 ± 0.35	81.87 ± 10.65
SB Granule	10	3.02 ± 0.44	32.99 ± 9.20	6.93 ± 0.62	79.61 ± 13.56
SB Granule	20	3.29 ± 0.40	36.28 ± 9.79	7.05 ± 0.52	81.05 ± 13.16

Note: group received Sea Buckthorn Granule comparison by control group P>0.05

Overview - The Conseco Brand Sea Buckthorn Granule

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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

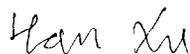
4. 3. 4. Aldrin ≤ 0.02 mg/kg

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

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



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