DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

1188 '03 MAR 13 P1:48

Date: March 7, 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: Asmakure
Firm: Port Orchard Nutriceuticals

Date Received by FDA: December 9, 2002

90-Day Date: March 9, 2003

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.

Thank you for your assistance.

Vickey Lutwak
CSO/Lead Reviewer

Attachments

95S-0316

RPT159

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Food and Drug Administration
College Park, MD

FEB 2 1 2003

1189 '03 MAR 13 P1:48

James Kao, B. Pharm, MBA
Junwei Sun, M.S., MBA
Port Orchard Nutraceuticals
1800 Sidney Avenue 1-203
Port Orchard, Washington 98366

Dear Mr. Kao and Mr. Sun:

This is to inform you that the notification you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on December 9, 2002. Your notification concerns the substances, Abies Webbiana 2.11%, Adhatoda Vasica 10.30%, Zingiber officinale 6.27%, Piper Longum 8.25%, Piper nigrum 4.07%, Cinnamomum Zeylanicum 1.00%, Ammomum Subulatum 1.00%, and Nisadal 1.00% under the name Asmakure, and Hemidesmus Indicus (Anantamul) 100 mg, Ricinus communis (Shetverenda) 100 mg, Moringa Pterygosperma (Sajina) 100 mg, Tinospora Cordifolia (Gulancha) 125 mg, and Boerhaavia Diffusa (Rakta Punarnaba) 75 mg under the name Panekure™ that you assert are new dietary ingredients.

The law at 21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce. This information must include the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the new dietary ingredient is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B), because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness and injury.

Federal regulations found at 21 CFR 190.6 specify the requirements for a premarket notification on a new dietary ingredient. The notification you sent us concerning the dietary supplements with tradenames Panekure™ and Asmakure does not comply with the requirements of 21 CFR 190.6 and is incomplete. For example it fails to:

- provide copies of the references to published information offered in support of the notification which shall be reprints or photostatic copies of such references, also, if any part of the material submitted is in a foreign language, it shall be accompanied by an accurate and complete English translation;

- sufficiently describe Panekure™ and Asmakure (e.g., identify the Latin binomial names of the botanicals (herbal ingredients) including the genus, species, and the (author) and any other known relevant properties of the botanical ingredient(s) and all relevant properties of the mineral ingredient Nisdal, including its chemical formula.

Accordingly, there is inadequate information in your notification for FDA to determine whether there is an adequate basis to conclude that the use of a dietary supplement that contains the ingredients identified in your notification will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains new dietary ingredient(s) for which there is inadequate information to provide reasonable assurance that it does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

If you wish, you may send us the required information and address the issues identified above to correct the deficiencies in your current notification in the form of an amendment in triplicate (i.e., an original and two copies). However, in order to serve as an amendment to the current notification, the information you submit must be delivered to this office by no later than February 22, 2003, which is 75 days after the current notification's filing date. We note that if the required information is not received within the 75-day timeframe, your notification will be filed in the FDA's Docket Management Branch 90 days from the effective filing date.

Another option is to send us at any time a new notification, in triplicate, that is complete and fully complies with 21 CFR 190.6. The date that we receive the additional information for either an amended or new notification is considered the new filing date. Please indicate in the cover letter if it is an amended or new notification.

Your notification will be kept confidential for 90 days from the date of the effective filing date. After the 90-day period, your notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. 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

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)

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

Sincerely yours,

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
and Compliance
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Pre-Marketing Notice

Division of Standards and Labeling Regulations
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, 20740-3835
Telephone Number: (301) 436-2371

Dear Director:

In accordance to the requirements of Section 413(a)(2) (21 U.S.C. 350b) of the Federal Food, Drug and Cosmetic Act, XXXX if filing for pre-marketing notice of new dietary ingredients in two Ayurvedic products (Asmakure and Panekure):

The new dietary ingredients are:

Asmakure:

1) **Abies Webbiana** is a high altitude herb found in the Himalayas with a very high anti-asthmatic property.
2) **Adhatoda Vasica** is a traditionally proven herb to combat bronchial disorders. The principals of this plant are alkaloids vasicine (mw 188, C11H12N20), vasicinone and vasicinol which are used as brochodialators.
3) **Zingiber officinale** is a herb containing essential oils like zingiberine and alpha-terpinone. These essential oils have potent anti-bacterial properties which reduce the acuteness of bronchial infection.
4) **Piper longum** is another kind of traditional herb whose active ingredient, monocyclic sesquiterpenes has counter irritant and analgesic properties for reducing muscular pain and inflammation. Previous research has found this to be effective in bronchial spasm and inflammation.
5) **Piper nigrum** is a medicinal herb which enhances anti-bacterial function and increases bio-availability of other herbs used in the formulation.
6) **Cinnamomum Zeylanicum** is the herb having depressant action on central nervous system (CNS) and thus, reduces stress induced asthma.
7) **Ammomum subulatum** is the herb which provides a soothing effect on broncho pharangial region and has a broncho sedative action.
8) **Nisadal** is a kind of white crystalline mineral substance which has mucolitic (i.e liquefying effect on dry cough) and expectorant (i.e expels liquefied cough) properties.

Panekure:

1) **Hemidesmus Indicus (Anantamul)** :Recent researches have proved exclusively that the active principles of this plant consist of an enzyme, an essential oil and a saponin. Rutin has been isolated from leaves. Detection of hexatriacontane, lupeol, its octa-cosanoate, mp. 81°, α - amyrin, β - amyrin, its acetate and sitosterol in roots by chromatography.
2) **Ricinus Communis (Shetverenda)** : Castor oil consists of the glycerides of ricinolcic, isoricinoleic, stearic and dihydroxy – stearic acids. Detection of palmitic (1.2), stearic (0.7), arachidic (0.3), hexadecenoic (0.2), oleic (3.2), linoleic (3.4), linolenic (0.2), ricinoleic (89.4%) and dihydrostearic acids as Me-esters in castor oil was done by GLC. The plant yields about 1% ricinine. Lupeol and 30 – norlupan – 3 β - ol – 20-one have been isolated from the coat of castor bean. Seed coat contained 1.50 – 1.62% lipids and higher amounts of phosphatides and non saponifiable matter than seed kernel.
3) **Moringa Pterygosperma (Sajina)** : A reddish brown oil called ptergospermin with strong antibiotic activity has been chemically isolated from this plant. Aldotriouronic acid from acid hydrolysis of gum has been characterised as O – (β – D – glucopyranosyluronic acid) (1 → 6) - β - D – galactopyranosyl (1 → 6) – D – galactose. Presence of aspartic acid, glutamic acid, glycine, threonine, alanine, valine, leucine, isoleucine, histidine, lysine, arginine, phenylalarine, tryptophan, cysteine and methionine have

been detected in leaves. Alanine, arginine, glycine, serine, threonine, valine, glutamic and aspartic acids have been detected in flowers and fruits; lysine in flowers, sucrose and glucose in flowers and sucrose in fruits. 4-hydroxy-mellein, vanillin, octacosanoic acid, β - sitosterol and β - sitostenone have been isolated from stems.

4) **Tinospora Cordifolia (Gulancha)** : Chemical analysis revealed that the plant contained an alkaloid, glycosides and sterol. An unidentified compound, mp. 114°, an amorphous compound, mp. 90°, a physiologically active unidentified compound, mp. 115°, a sterol, mp. 134° and a fatty acid, mp. 84°, have been isolated from the plant. Al diterpenoid of columbin type – tinosporin (0.02%), mp. 184° and tinosporide mp. 236° and cordifolide, mp. 176° have also been isolated from the plant. Tinosporidine and β - sifosterol have been isolated from stems; and cordifol, heptacosanol and octacosanol from leaves. A new furanoid diterpene – tinosporide has been isolated from stems.

5) **Boerhaavia Diffusa (Rakta Punarnaba)** : Chemical analysis reveals the presence of an alkaloid and an oily mass. Sulphates, chlorides and traces of nitrates and chlorates are obtained from the ash. Ash (11.8), Ca (1.2) and K 2.3%), presence of alkaloids, free and combined amino acids have been determined in aerial parts of the plant. Boerhaavic acid, low tannins, phlobaphenes, reducing sugars (glucose), and 0.01% of a crystalline base named punarnavine were also isolated. Hexa-triacontane, β - sitosterol and ursolic acid have been isolated from roots, a polysaccharide was isolated which on hydrolysis yielded glucose, xylose, glucuronic acid, galactose, L – avabinose and L – rhamnose; a glycoprotein with a molecular weight of 16,000 – 20,000 daltons was isolated from roots.

All the relevant in vivo and clinical information is enclosed. These new dietary ingredients will not be marketed in the US for 75 days after your expected receipt of this Notice

Yours truly,

James Kao, B.Pharm, MBA

Junwei Sun, M.S., MBA

Port Orchard Nutraceuticals
1800 Sidney Ave 1-203
Port Orchard, WA
98366

Mr. Jame Kao
1-360-874-6958
Called 12/19 + left message that
notification was incomplete

HERBICURE PRIVATE LIMITED
Metro Garden City, Pailan, 24 PGS(S)

PANEKURE™
(A herbal research medicine)

Each Capsule Contents :

Hemidesmus indicus	100 mg;
Recinus communis	100 mg;
Moringa pterygosperma	100 mg;
Tinospora cordifolia	125 mg;
Boerhaavia diffusa	75 mg;
Exepient (filler)	QS

Indication :

Oesteoarthritis, pain, inflammation, ankylosis, cervical spondylosis, arthralgia, myalgia, synositis.

1) Panekure inhibits prostaglandians synthesis by COX2 inhibition.
2) Panekure does not induced gastric or intestinal ulceration. Moreover, it promotes secretion of cytoprotective mucus in the intestine and prevents mucosal damage.
3)
4) Panekure has no damaging effect on kidneys.
5) Panekure is non-toxic and a very safe herbal medicine treatment by Panekure may be safely continued for any length of time.

Dose :

1 – 2 capsule thrice a day or as directed by the physician.

Properties of Ingredients :

1) Hemidesmus indicus possesses a very good anti-inflammatory properties (Ref.1).
2) Ricinus communist has pain cure activity (Ref. 2).
3) Moringa pterygosperum is useful in fever and pain (Ref. 3).
4) Tinospora cordifolia is used as anti-inflammatory agents (Ref. 4).
5) Boerhaavia diffusa is useful in controlling pain and inflammation (Ref. 5).

References :

1) Indigenous Drugs of India 2nd ed. 1982, Academic Publisers, p.188.
2) Ibid, p.236.
3) Ibid, p.364.
4) Ibid, p.426
5) Ibid, p.494

HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

TOXICOLOGICAL DATA OF PANEKURE IN S – D RATS IN P. O. ROUTE FOR 6 WEEKS

Route P. O. (Per OS)

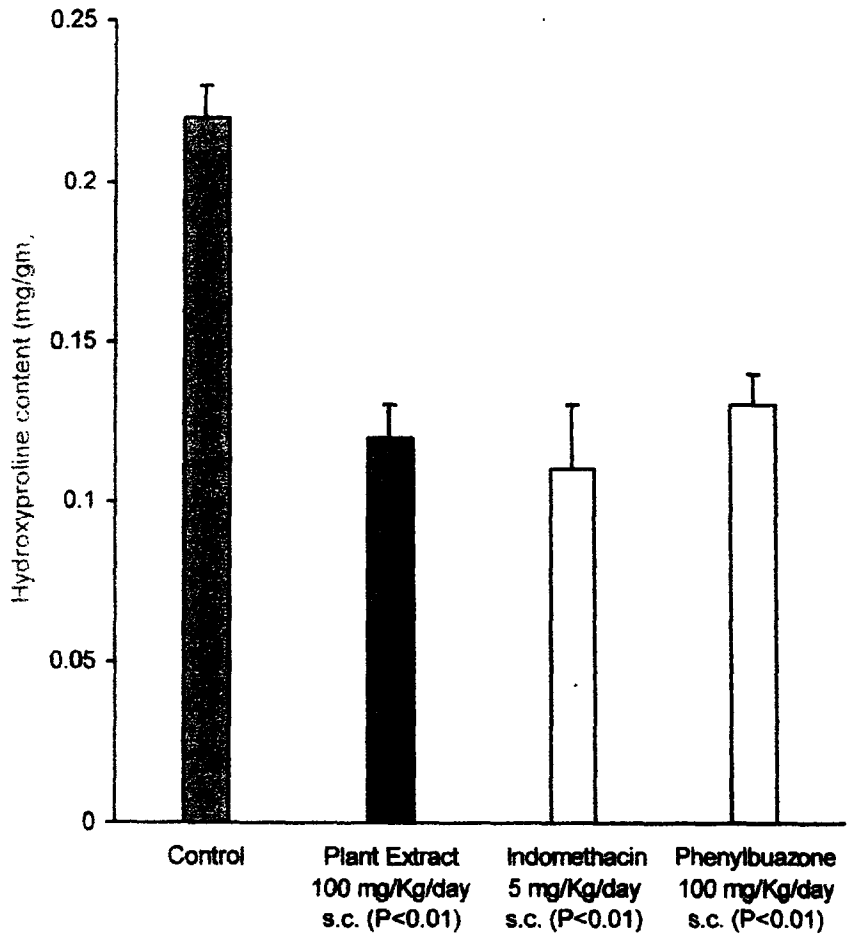
For 6 Weeks

Sl. No.	Parameters	Normal (Saline Control)	Treated (Panekure)
A.	**Haematological Test :**		
(1)	Erythrocyte Value of Rat (million / dl)	8.9 (7.2 – 9.6)	8.8 (7.3 – 9.5)
(2)	Hemoglobin (gm / 100 ml)	14.8 (12.0 – 17.5)	14.7 (12.1 – 17.4)
(3)	Plateles : Thousands/dl of blood	1240 (1100 – 1380)	1200 (1050 – 1240)
B.	**Liver Function Test :**		
(1)	Cholesterol (mg/100 ml blood)	127.5 ± 2.0	120.5 ± 1.9
(2)	Bilirubin Total (mg/100 ml blood)	0.48 ± 0.1	0.49 ± 0.2
(3)	SGOT Unit/ml Serum	89.4 ± 3.0	90.2 ± 4.0
(4)	SGPT Unit/ml Serum	33.2 ± 1.9	35.5 ± 1.8
C.	**Kidney Function Test :**		
(1)	Creatinine Clearance ml/min	10.1 (6.3 – 15.2)	11.2 (7.5 – 16.0)
(2)	Urea Clearance ml/min/m2	14.4 (3 – 28)	15.5 (4 – 29)

HERBICURE PRIVATE LIMITED

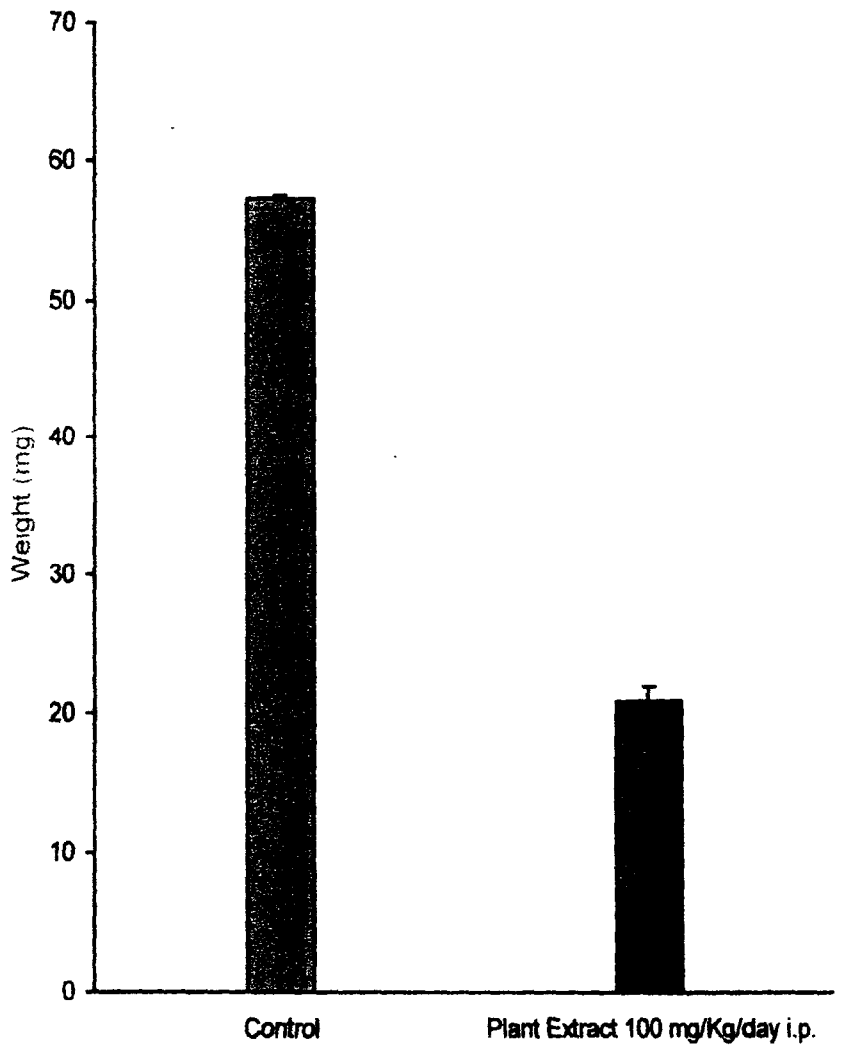
Factory: Metro Garden City, Pailan, 24 PGS(S)

Effect of plant extract of **PANEKURE**, Phenylbutazone & Indomethacin on the hydroxyproline content of carrageenin induced granuloma tissue in rats.



HERBICURE PRIVATE LIMITED
Factory: Metro Garden City, Pailan, 24 PGS(S)

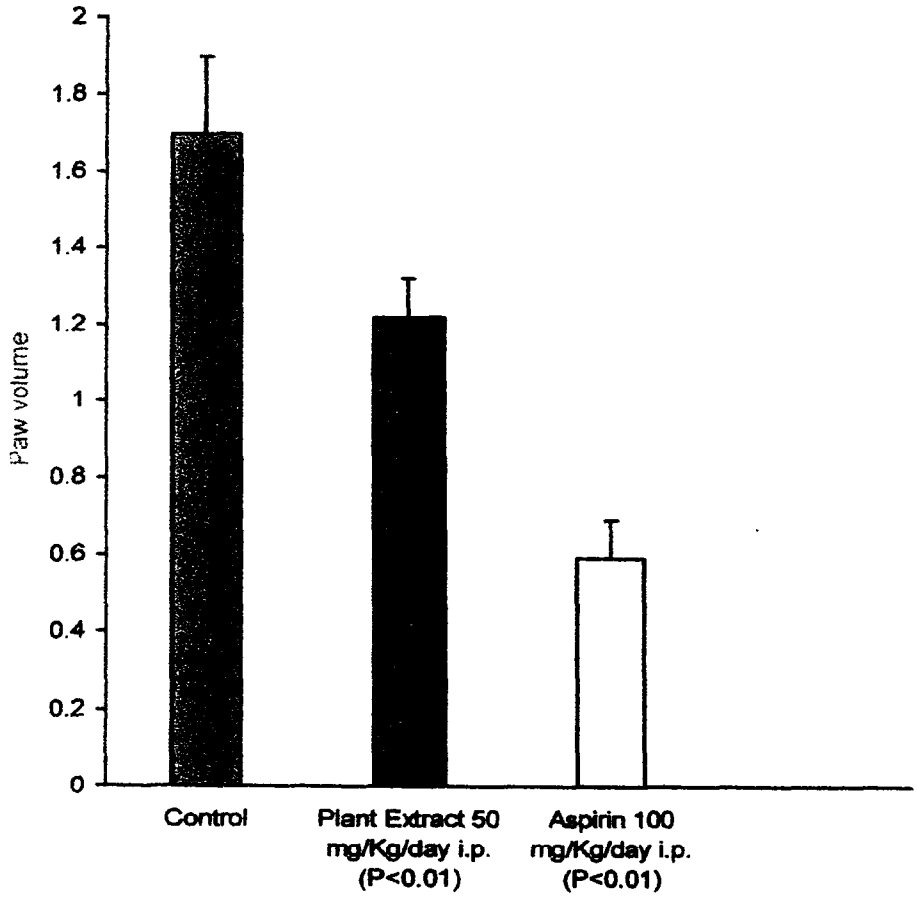
Effect of plant extract of PANEKURE on peroxide (glucose oxidase) induced inflammation.



HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

Effect of plant extract of PANEKURE and Aspirin (ref. standard) on right hind paw of adjuvant induced arthritis rats.



HERBICURE PRIVATE LIMITED
Factory: Metro Garden City, Pailan, 24 PGS(S)

A BRIEF ON ASMAKURE

Herbicure's anti-asthmatic herbal medicine, called **Asmakure**, has been developed by the Department of Pharmaceutical Technology, Jadavpur University after a prolonged and rigorous R&D spanning more than 7 years. During the research work, very large base of pre-clinical studies and post-clinical observations were carried out to reveal non-toxic effect of the medicine with high therapeutic value in asthmatic disorder.

A collaborative effort between Herbicure and Jadavpur University has brought an amazing ayurvedic medicine, called Asmakure, under Indian School of Medicine (ISM), which aims at permanent relief of the patients from the agony of asthma.

Compositions:

As far as the formulation of the medicine is concerned, Asmakure is very different from those of other prevalent ayurvedic medicines. While the similarity generally found between Asmakure and the others is only *Adhatoda Vasica*, other ingredients in Asmakure are completely different. Asmakure is composed of eight established herbs which all have unique multi-dimensional therapeutic values as follows :

1. ***Abies Webbiana*** is a high altitude herb found in the most difficult terrains of Himalayas with a very high anti-asthmatic property. Herbicure has permanent arrangement for uninterrupted supply of this most potent herb from Himalayas.

2. ***Adhatoda Vasica*** is traditionally proven herb to combat bronchial disorders. The principals of plant are alkaloids vasicine (mw 188, C_{11} H_{12} N_{20}), vasicinone and vasicinol which are used as brochodialators.

3. ***Zingiber officinale*** is a herb containing essential oils like zingiberine and alpha-terpinone. These essential oils have potent anti-bacterial properties which reduce the acuteness of bronchial infection.

4. ***Piper longum*** is another kind of traditional herb whose active ingredient, monocyclic sesquiterpenes has counter irritant and analgesic properties for reducing muscular pain and inflammation. Thus, found in research most effective in bronchial spasm and inflammation.

5. ***Piper nigrum*** is a medicinal herb which enhances anti-bacterial function and increases bio-availability of other herbs used in the formulation.

6. ***Cinnamomum Zeylanicum*** is the herb having depressant action on central nervous system (CNS) and thus, reduces stress induced asthma.

7. ***Ammomum subulatum*** is the herb which provides soothing effect on broncho pharangial region and has a broncho sedative action.

8. ***Nisadal*** is a kind of white crystalline mineral substance which has mucolitic (i.e lequifying effect on dry cough) and expectorant (i.e. expels lequified cough) properties.

Formulations

Research has revealed that most of the medicinal plants have a tendency to hydrolise in presence of water which reduces the therapeutic efficacy. While some ayurvedic medicine is formulated in syrup form (water base), Asmakure is formulated in dry-dry powder form keeping moisture content less than 4% to avoid any possible hydrolysis and thus, to increase its shelf life. In liquid base, synthetic preservative is generally used to avoid microbial growth and all these synthetic preservatives are prone to toxicity leading to asthmatic attack. But in Asmakure, there is no use of any preservative or synthetic additive and has been kept in natural form.
Further, any pH shift can precipitate out some active ingredients from the syrup base, which is ruled out in Asmakure for its dry-dry powder form.

Mode of Action of Asmakure vis-à-vis other prevalent anti-asthmatic ayurvedic medicines

Asthma is a chronic inflammatory disorder of airway. Mast Cells are releasing various inflammatory mediators like prosta-glandins, leukotrienes, cytokine and histamines. All are broncho-constrictors and released due to disintegration of mast cell. While the prevalent herbal medicines aim at only single mediator called leukotrienes, Asmakure covers all mediators which act as broncho-constrictors and it mainly performs as mast cell stabilizer and thus, prevents the release of inflammatory mediators which lead to various kinds of asthmatic attack. Asmakure, thus, has approached the root of the asthmatic disorder and aims at permanent protection.

Apart from the above, Asmakure has a strong anti-bacterial mucolytic and expectorant action and thus, offering a complete package of relief to asthmatic patients and even those suffering from common cold and cough, and bronchitis.

Step down approach

Asmakure has been designed in such a way so as to ensure assured result with sustained use of the prescribed dosage which brings down even the steroid taking patients to the level of normal breathing and tranquility. Regular use of Asmakure along with pure honey at least for a period of six months also provides immunity to the asthmatic patients.

Clinical Trial

The clinical trial of Asmakure was carried out by the State Ayurvedic Medical College & Hospital. The drug was administered orally among 32 patients (age between 12-55 years of either sex, male 20 and female 12) for consecutive 28 days. The report concludes *"clinical results revealed that most of the patients who were suffering from bronchial asthma, and chronic dry cough, got relief from asthma complications due to Ayurvedic drug, Talishadi-herbi (Asmakure). The patients' compliance of the drug was satisfactory and it can be strongly recommended that the drug can be very useful in asthmatic management."*

Patent of Asmakure

Keeping in view the inventions made towards the process management of the various extracts of active ingredients of the herbs used in the formulation of Asmakure and the exclusivity of Abbies Webbiana, in particular, Herbicure has applied for domestic as well as international patent of the product.

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HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

Annexure - I

PRODUCT DATA SHEET

Presentation Dry-Dry Powder in 100gm bottle.

Uses- Effective against allergic Bronchitis and Asthma. Also brings relief in common cold and persistent cough.

Doses- 1-2 tsf twice daily.

Administration- Administration through P.O. along with honey.

Contra-indication : Nil

Use in pregnancy and lactation: Not yet established.

Side-effects: No known side effect.

Precaution: Sudden withdrawal of any existing medication (anti asthmatic) is advised against.

Warning: Not found.

Absorption: Good.

Fate: Metabolism, partly through first by pass.

Distribution: Apparent volume distribution (vd) is moderate.

Metabolism: Mainly by liver cells.

Excretion: Entrance excretion through high pH (alkaline) urine.

Elimination: Related with urinal pH.

Package Quantity: 60 bottles (each of 100 gm) in a single carton.

HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

Annexure - II

TECHNICAL DATA

a) Acute test (single dose). Test in which single doses of the drug are used on each animal on one occasion only for determination of LD_{50} or Median Lethal Dose (MLD), i.e. the dose which will kill 50% of the animals of a particular species. LD_{50}value is determined in a 24 hour test using two species (mice or rats) and one non rodent (usually rabbits).
Acute toxicity studies of ASMAKURE in animals studies revealed:

i) Even a very high dose in animal by p.o. route did not produce any mortality in rats and or rabbits. So, there is no question of LD_{50} value determination. Behavioral patterns (like motor activity, CNs stimula dep.) were also unaffected due to Asmakure.

Subacute test (daily dose): Tests in which animals (usually rats) are given dose daily starting at around expected therapeutic level and increasing stepwise every two to three days until toxic signs are observed. Hematological and biochemical monitoring are carried out. After 2-4 weeks pathological and histological examination are dose after killings the animals.

Subacute toxicity studies of ASMAKURE in rats for 4 weeks revealed:

1) Dose in oral route (P.O.) was well tolerated by the animals for continuous 4 weeks treatment.

2) There were no haematological abnormalities in animal due to ASMAKURE treatment. Hb, WBC, RBC were unchanged and there was no depression of bone marrow due to the herbal medicines.

3) Liver function tests were also unaltered due to Asmakure SGOT SGPT. Bilirubin level of treated rats were within limit after subacute treatment with Asmakure. Histological findings confirmed about unaltered liver cells architecture.

b) Mutagenicity studies revealed that the herbal drug ASMAKURE is totally free from any mutagenic effect.

c) If the drug is to be used in women of child- bearing age, its effect on fertility as well as its teratogenic potential must be investigated. Asmakure was tested on pregnant rats extensively for conformation of its safety in women of child-bearing age. However, we have not performed the clinical test on human subject to find say the drugs safety in pregnancy.

d) Other find toxicological studies, like kidney function tests also confirm the drug's safety.

HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

Annexure – III

PHARMACOLOGICAL DATA

1) Human Pharmacokinetic and metabolism.

   a) The drug is acidic in nature. So its ionization in gastric pH is less (low pk value). The drugs absorption of gastric region is very high.

   b) Oral absorption is very good and bio availability is also good.

   c) Apparent volume distribution(Vd) is moderate.

   d) Half life(t ½) : 10-12 hrs.

   e) Biotransformation: Through hepatic enzyme.

   f) Heptic/renal failure: Dose should be adjusted in hepatic or renal failure patients.

   g) Au: Elimination of drug in alkaline urine (high pH) is high.

2) Studies mainly done on mast cell stabilization and bronchodilatation activity in animal to establish the drug's anti-asthmatic value.

3) Secondary pharmacological action like mucolytic and expectoration action of the drug has confirmed its action as mucolytic expectorant.

4) Drug Interaction Studies: There was no such drug interactions found with modern antiasthmatic drugs.

HERBICURE PRIVATE LIMITED

Factory: Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

ANNEXURE – IV

TECHNOLOGICAL DATA – 'A'

COMPOSITION FORMULA OF ASMAKURE

Sl#	INGREDIANTS	% COMPOSITION
1	ABIES WEBBIANA (TALISHPATRA)	2.11
2	ADHA TODA VASICA (VASAK)	10.30
3	CINNAMOMUM ZEYLANICUM (DARUCHINI)	1.00
4	AMMOMUM SUBULATUM (BARA ELAICHI)	1.00
5	PIPER NIGRUM (GOLMORICH)	4.07
6	PIPER LONGUM (PIPUL)	8.25
7	ZINGIBER OFFICINABLE (ADA)	6.27
8	NISADAL	1.00
9	SUGAR	66.00

HERBICURE PRIVATE LIMITED

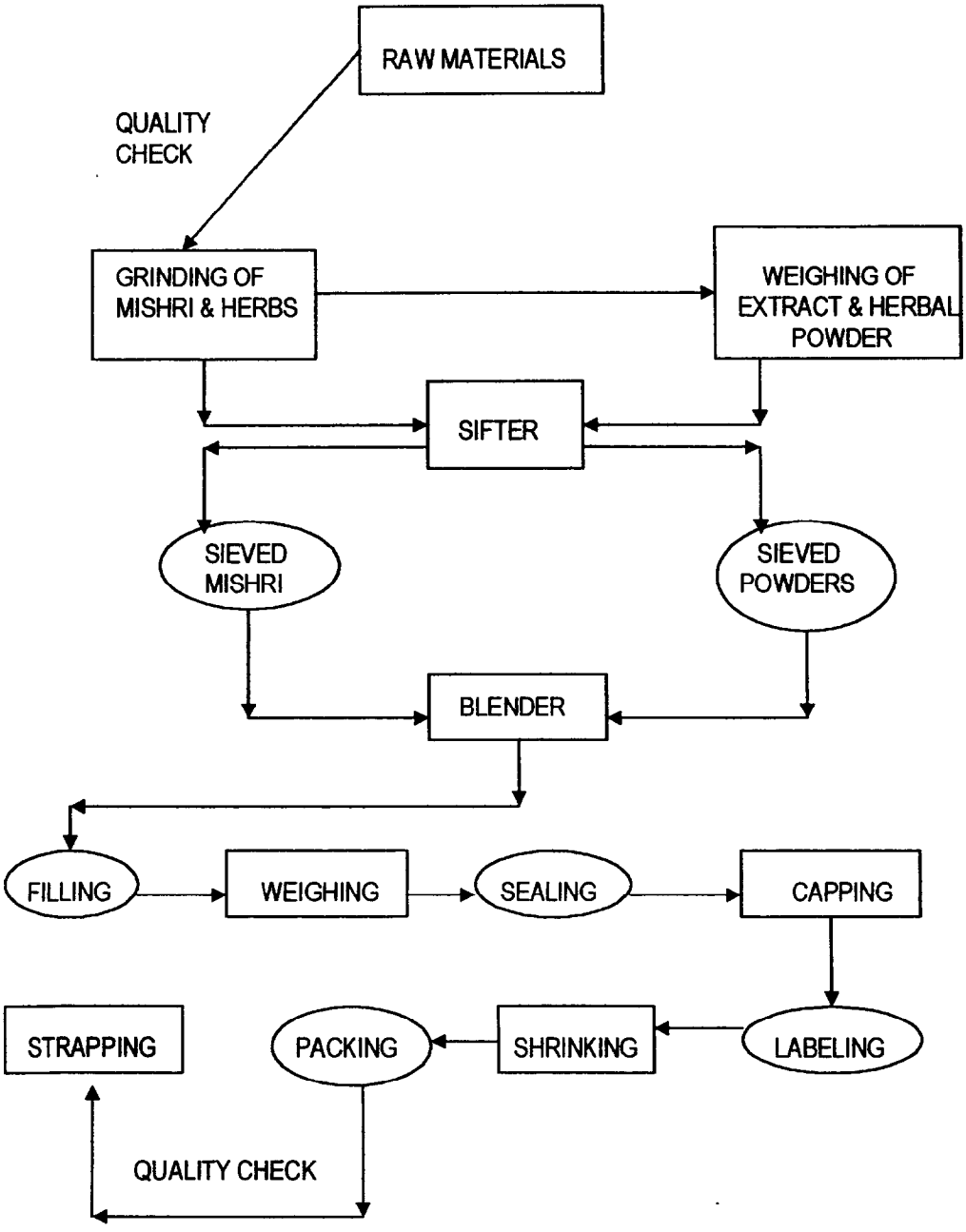
Factory: Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

ANNEXURE – IV

TECHNOLOGICAL DATA – 'B'

MANUFACTURING INSTRUCTIONS FOR ASMAKURE PRODUCTION



HERBICURE PRIVATE LIMITED

Factory : Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

ANNEXURE – IV

TECHNOLOGICAL DATA – 'C'

CONTROL DATA FOR THE ACTIVE CONSTITUENTS OF ASMAKURE

S#	ACTIVE CONSTITUENTS	REMARKS
01	**ALKALOIDS** i) VASICINE ii) PIPERINE iii) PIPERLONGUMINE iv) PIPERLONGUMININE	PRESENT WITHIN LIMIT
02	**VOLATILE OILS** i) EUGENOL ii) CINEOLE ZINGIBEROLE	PRESENT WITHIN LIMIT
03	ESSENTIAL OILS	PRESENT WITHIN LIMIT
04	TERPENES	PRESENT WITHIN LIMIT

HERBICURE PRIVATE LIMITED

Factory : Metro Garden City, Pailan, 24 PGS(S)

ASMAKURE

ANNEXURE – IV

TECHNOLOGICAL DATA – 'D'

CONTROL DATA FOR FINISHED PRODUCT (ASMAKURE)

01		TOTAL WEIGHT OF THE SAMPLE	:	NLT 100 GM.
02		MESH SIZE	:	99% THROUGH 20 #
03		SOLUBILITY (IN WATER)	:	NLT 69%
04		pH OF ASMAKURE SOLUTION		
	i)	10% (W/V) SOLUTION IN WATER	:	4.0 TO 4.8
	ii)	20% (W/V) SOLUTION IN WATER	:	4.0 TO 4.8
	iii)	30% (W/V) SOLUTION IN WATER	:	4.0 TO 4.8
	iv)	1% (W/V) SOLUTION IN WATER	:	4.0 TO 6.0
05		MICROBIAL COUNT	:	10000 CFU/GM.
06		TEXTURE	:	COARSE POWDER
07		COLOUR	:	LIGHT BROWN
08		TASTE	:	SWEETISH, PUNGENT, HEATING
09		ODOUR	:	SWEET PUNGENT
10		L.O.D.(% W/W AT 105°C)	:	NMT 5 %
11		BULK DENSITY	:	NLT 0.75 GM/C.C.
12		REFERENCE	:	AYURVEDIC PHARMACOPEIA AND INDIAN PHARMACOPEIA

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ASMAKURE

ANNEXURE – IV

TECHNOLOGICAL DATA – 'E'

STABILITY DATA AND PROPOSED SHELF-LIFE OF FINISHED PRODUCT (ASMAKURE)

THE STABILITY STUDIES OF THE DRUG WAS CARRIED OUT AT THE THREE TEMPERATURES NAMELY 37°C, 40°C & 50°C AND IT WAS FOUND TO BE STABLE.

THE SHELF LIFE OF THE DRUG HAS BEEN PROPOSED TO BE THREE YEARS FROM THE DATE OF MANUFACTURING AS MENTIONED IN THE LABEL.

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ASMAKURE

Annexure - V

CLINICAL DATA **

(Reference No.JBR/PS-19/2001 Dt: 19/02/2001)

a) **Phase I Clinical Trial Report** :

The drug (Asmakure) was administered orally to a number of patients(Age between 12-55 years of either sex, male 20, female 12) who were suffering from asthma, in the done range of 1-2 teaspoonful twice daily (B.D.) with honey for 28 days consecutively day.

Clinical trial revealed that, most of the patients who were suffering from bronchial asthma, and chronic dry cough (non productive cough) got relief from asthma complication due to this Ayurvedic drug. In most of the cases, it has been found that the drug has a definite expectorant action.

The patients compliance of the drug was satisfactory and it can be strongly recommended that Asmakure can be very useful in asthma management.

b) **Phase II Clinical trial** :

Not done.

c) No side effect /adverse reactions was found in human subject who received the drug for 28 days consecutively.

d) Report on clinical and pharmacological studies are in process for publication.

Name & Address of the Investigator :

Dr. Gopal Chandra Sengupta
Principal – Superintendent
J. B. Roy State Ayurvedic Medical College & Hospital
Kolkata, West Bengal

** As per recent guidelines of WHO, the Ayurvedic medicines require less stringent Clinical Trials to go through since these medicines are based on time-tested traditional practice spread over a long period of time.

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Table-I

Effect of Asmmakure on different symptoms and signs of Asthma

Sl No.	Symptoms	Treatment with Placebo	Present before treatment	After treatment (No. of relief / total patient)			
		Symptoms / total patients		1st	2nd	4th	8th
1.	Proxysmal Dyspnoea	7 / 10	40 / 50	20 / 50	10 / 50	10 / 50	8 / 50
2.	Feeling of lightness in chest	10 / 10	50 / 50	10 / 50	10 / 50	5 / 50	0 / 50
3.	Hoarseness in voice	5 / 10	25/ 50	5 / 50	5 / 50	4 / 50	1 / 50
4.	Cough	10 / 10	50 / 50	10 / 50	5 / 50	5 / 50	5 / 50
5.	Ronchi	8 / 10	40 / 50	8 / 50	6 /50	3 / 50	0 / 50
6.	Difficulty of expectoration	8 / 10	30 / 50	0 / 50	0 / 50	0 / 50	0 / 50

Table-II

(BTPS)
Sprirometry Study Report of Asmakure Treatment

Parameters	Treatment with placebo	Asmakure Treated Group			
		1st Week	2nd Week	4th Week	8th Week
FEV(L)	1.44 ± 0.02	1.50 ± 0.01	1.75 ± 0.01	1.95 ± 0.02	2.10 ± 0.01
P value	> 0.5	> 0.05	> 0.5	> 0.5	> 0.5
Lung Volume IC (L)	4.23 ± 0.01	4.44 ± 0.09	5.5 ± 0.1	5.6 ± 0.01	5.7 ± 0.02
P value		< 0.001	< 0.001	< 0.001	< 0.001

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Table-III

Effect of Asmnakure on Respiratory Rate of Asthma Patients

Treatment with placebo	Treatment with Asmakure			
	1st Week	2nd Week	4th week	8th week
25.0 ± 1.9	21.07* ± 1.2	18.72* ± 0.01	18.52* ± 0.02	17.97* ± 0.05
P values	< 0.05	< 0.001	< 0.05	< 0.001

Table-IV

Effect of Asmnakure on vital capacity of patients of Asthma

Treatment with placebo	Treatment with Asmakure			
	1st Week	2nd Week	4th week	8th week
1230 ± 10.50	1570 ± 9.3	1680 ± 11.5	1930 ± 13.2	2100 ± 7.3
P values	< 0.001	< 0.001	< 0.001	< 0.001

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Table-V

Prick Test
(Skin Testing with different Allergens to the Patients received Asmakure)

Types of Allergens	Treatment with placebo	Treatment with Asmakure			
		1st Week	2nd Week	4th Week	8th Week
Cotton	+	+*	-	-	-
Hay	+	+	-	-	-
Mixed grain	+	+	-	-	-
Dog (furs)	+	+	-	-	-
Cat (furs)	++	++	-	-	-
Rabbit (furs)	++	++	+	-	-
Ship wool (fabric)	++	++	+	-	-
Egg	++	+	-	-	-
Milk	+	+	+	-	-
Grass (pollen)	++	++	+	-	-
Cheese	++	++	-	-	-

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Table-VI

Biochemical Changes to the Patients who received Asmakure for 8 Weeks Continuously

Parameters	Treatment with placebo (No. of Patients 10)	Treatment with Asmakure (No. of Patients 30)
Hematological		
Haemoglobin	12 ± 4 gm/dl.*	13 ± 2 gm/dl.*
Red cell count	4.3 ± 0.1x 10^6 / ul*	4.5 ± 0.2x 10^6 / ul*
MCHC	30 ± 9%*	33 ± 8%*
Eosinophil	13 ± 0.1%	6 ± 0.01%**
ESR	22 ± 1 mm/hr.	20 ± 2 mm/hr.
Glucose tolerance	175 ± 5 mg/100 ml	175 ± 7 mg/100 ml+*
Liver Function Test		
Bilirubin (Total)	0.1 ± 0.2 mg/dl.	0.1 ± 3 mg/dl.*
Protein (Total)	6.0 ± 1 gm/dl.	6.1 ± 9 gm/dl.*
SGOT	14 ± 4 units/ml.	12 ± 3 units/ml.*
SGPT	20 ± 4 units/ml	19 ± 8 units/ml.*
Kidney Function Test		
Creatinine	80 ± 8 umol/l	78 ± 4 umol/l*
Creatine	40 ± 7 umol/l	38 ± 4 umol/l*