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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-388

Pharmacology Review(s)

MEMORANDUM

Date: January 3, 2003
From: John K. Leighton, Ph.D., DABT
Supervisory Pharmacologist, HFD-150
To: File for NDA #21-388
Re: Approvability for Pharmacology and Toxicology
Sterile Talc

Background:

Sterile talc is indicated for the [redacted] Sterile Talc is currently delivered as an aerosol formulation. In the current NDA application the sponsor is proposing a change to a slurry formulation. The new formulation does not expand the use of sterile talc, and the local delivery does not represent any new concerns over systemic toxicity. The few animal studies conducted with the slurry formulation (available in the public literature) were adequately reviewed by Drs. Schmidt and Goheer. There are no new safety concerns raised in the nonclinical studies by the change in formulation.

Dr. Goheer recommended that the information [redacted] be removed from the proposed label. The submission does not contain adequate study information to support the conclusions regarding [redacted] for sterile talc. I concur with his request.

Recommendations:

The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues.

APPEARS THIS WAY
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/s/

John Leighton
1/3/03 03:52:47 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-388
Review number: 1 (Label review included)
Sequence number/date/type of submission: 000 / 9-20-2002 / NDA
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Waldman Biomedical Consultancy, Inc., P.O. Box 575, Oceanside, New York
for
Bryan Corporation, Four Plympton Street, Woburn, MA 01801.
Manufacturer for drug substance: [redacted]

Reviewer name: M. Anwar Goheer, Ph.D.
Division name: Division of Oncology Drug Products
HFD #: 150
Review completion date: January 3, 2003

Drug: Sterile Talc Powder
Trade name: Talc USP, Ultra Talc 2000
Generic name (list alphabetically):
Code name: N/A
Chemical name: Hydrated magnesium silicate
CAS registry number: Talc: 14807-96-6
Mole file number: N/A
Molecular formula/molecular weight: $Mg_3Si_4O_{10}(OH)_2$ / 379.3

Relevant INDs/NDAs/DMFs: NDA 20-587 approved on December 24, 1997.
Drug class: Sclerosing agent
Indication: Treatment of malignant pleural infusions secondary to malignancies having spread to the pleural space.

Clinical formulation: Talc USP contains asbestos-free talc and chlorite at a concentration of greater than 95%. Associated minerals include dolomite, calcite, and quartz.
The particle size of the powder is [redacted]

Route of administration: Intrapleural via chest tube

Previous clinical experience: Yes, see NDA 20-587

Previous Review(s), Date(s) and Reviewer(s):

Review #	Date	Reviewer
1	10-27-95	W.J. Schmidt, Ph.D.
2	2-26-96	

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: This NDA for Sterile Talc Powder is approvable from a Pharmacology/Toxicology perspective with label changes as describe under Recommendation on Labeling.

B. Recommendation for Nonclinical Studies: Studies for Sterile Talc Powder were summaries from literature references only.

C. Recommendations on Labeling: See label changes under Recommendation on Labeling.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: This NDA is based on published literature references. The sponsor has not performed any non-clinical pharmacology or toxicology studies. From the published experiments, intrapleural injection of 400 mg/kg talc slurry in rabbits produced pleurodesis 28 days after the injection (Lung 1998;176:299). Werebe et al. (Chest 1999;115:190) had reported the distribution of talc in every organ of the body after intrapleural administration in normal rats. The addition of iodide or intrapleural air did not effect pleurodesis in rabbits (Chest 1998;114:1143).

B. Pharmacologic Activity: Sterile Talc Powder is the non-aerosol version of Sclerosol® Aerosol Sterile Talc Powder (NDA # 20-587). It can be administered at bedside through a chest tube. Talc has been used to control pleural effusion for many years. The mechanism by which talc produces a pleurodesis after the intrapleural administration is not completely understood. Its therapeutic action is due to its adsorption onto the pleura. The resulting inflammatory process prevents re-accumulation of pleural fluid. This action may result in the relief of symptoms of malignant pleural effusions. The NDA under review changes the method of administration from aerosol (— to slurry — g). Limited nonclinical pharmacology studies available from the published literature indicate that no safety concerns arise from the new method of administration.

C. Nonclinical Safety Issues Relevant to Clinical Use: No information is available on impairment of fertility in animals by talc.

III. Administrative

Reviewer signature: /S/

Supervisor signature: Concurrence - _____

Non-Concurrence - _____

cc: list:

Division File
LeightonJ
ScherN
BradleyS
Goheer

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

1. Xie, C. et al. Serial observations after high dose talc slurry in the rabbit model for pleurodesis. Lung 1998;176(5):299-307.

Sixty-six rabbits received 400 mg/kg talc slurry by intrapleural injection. Ten to 12 rabbits were sacrificed 1, 2, 4, 7, 14, and 28 days after the treatment. At sacrifice the pleural fluid was measured and pleural surfaces were examined grossly and microscopically.

Talc was present in all animals at the time of sacrifice. There was a clinically significant pleurodesis in all animals on day 28 but not day 14. There was a progressive increase in the gross and microscopic fibrosis over the 28 days.

2. Werebe, EC. et al. Systemic distribution of talc after intrapleural administration in rats. Chest 1999;115(1):190-3.

Forty rats were divided into two groups. Group 1 received 20 mg of talc (extrapolated from the usual dose of 5 g in a 70-kg adult man) through a catheter placed in a left minimal thoracotomy. Second group received 10 mg talc. Half of the animals in each group were killed 24 hours and the remaining half 48 hours after the treatment. Lungs, chest wall, liver, kidneys, spleen, heart, and brain were examined microscopically.

Talc crystals were found in every organ of all animals. There was no statistical difference either on the dose of the talc used or in the time of death. The clinical significance of this finding is unknown.

3. Mitchem, RE. et al. Pleurodesis by autologous blood, doxycycline, and talc in a rabbit model. Ann Thorac Surg 1999;67(4):917-21.

Twelve NZ white rabbits (~4 kg body weight) received uncoagulated autologous blood (1 mL/kg), 6 animals received doxycycline (10 mg/kg), 8 animals received sterile talc slurry (70 mg/kg), and 4 animals received a chest tube only. Thirty days after the treatment, animals were sacrificed and pleural surfaces were graded by gross observation and histologic examination. Blood (clinical chemistry and ACE) and lung tissues were analyzed to determine systemic effects.

Doxycycline produced effective pleurodesis with severe local effects. Talc-treated animals exhibited effective pleurodesis. New vascular endothelial activity could account for part of the elevated ACE concentration in the talc test animals. Histological changes in the contralateral lung and enzymes elevation were observed after treatment with doxycycline and talc, suggesting systemic effects. Liver transaminases were increased (~ 2 fold) in doxycycline-treated animals and talc treatment increased ACE (~ 2 fold) both in serum and lung homogenate as compared to chest tube treatment. Autologous blood was only slightly more effective than a chest tube alone.

4. **Cohen, RG. et al. Talc pleurodesis: talc slurry versus thoracoscopic talc insufflation in a porcine model. Ann Thorac Surg 1996;62(4):1000-2.**

On one side of eleven immature pigs (weight 35-50 kg), a slurry of 5 g sterile USP talc was instilled through a thoracostomy tube. On the other side, the lung was deflated and 5 g of dry talc was insufflated under thoracoscopic visualization. The animals were sacrificed 30 days later and the quality of pleural adhesion was graded.

There was no difference between the techniques for density of adhesion scores (talc slurry 9.9±2.2 vs. thoracoscopic talc insufflation 10.0±2.5) or distribution of adhesion score (talc slurry 5.5±1.0; thoracoscopic talc insufflation 5.8±0.4). Both methods produced effective pleurodesis in the porcine.

5. **Colt, HG. et al. A comparison of thoracoscopic talc insufflation, slurry, and mechanical abrasion pleurodesis. Chest 1997;111(2):442-8.**

Ten mongrel dogs (weight 25-35 kg) were randomly assigned to receive two of four methods of pleurodesis: (1) dry gauze abrasion through a limited thoracotomy; (2) thoracoscopic mechanical abrasion using a commercially available 5-mm stainless steel grooved burr abrader; (3) thoracoscopic talc insufflation (TTI) using 4 g of asbestos-free USP approved sterile talc powder administered by pneumatic atomizer; and (4) instillation of talc slurry comprising 5 g of USP approved sterile, asbestos-free talc powder suspended in 100 mL of sterile saline solution. Animals were killed 30 days after treatment. The efficacy of pleurodesis was graded by evaluating the gross appearance of each pleural cavity and lung (pleurodesis score) and by determining the extent of adhesion formation (obliteration grade).

TTI produced a greater degree of parietal and visceral pleural fibrosis than mechanical abrasion in the canine model. No differences in obliteration grade were demonstrated between talc administration techniques and mechanical gauze abrasion.

6. **Xie, C. et al. Comparisons of pleurodesis induced by talc with or without thymol iodide in rabbits. Chest 1998; 113(3):795-9.**

New Zealand white rabbits were randomly assigned to receive talc slurry (200 mg/kg, approximately three times that used for treating recurrent pleural effusion or pneumothorax in humans) with or without the addition of 50 mg iodide intrapleurally. Approximately 10 rabbits in each group were killed 1, 2, 4, 7, 14, and 28 days after the injection. Pleural adhesions and microscopic changes were compared.

The pleural fluid findings, the gross adhesion score for the pleura, and the microscopic changes in the visceral pleura were essentially the same for both groups. The mean degree of gross pleurodesis in the talc group on day 28 was 2.6±0.2 compared with 2.3±0.2 in the iodized group. The mean degree of microscopic fibrosis was 1.4±0.3 in the plain talc group compared with 2.0±0.3 in the iodized talc group. The addition of 50 mg iodide did not effect pleurodesis in rabbits. Human studies had shown similar pleurodesis with iodized and non-iodized talc.

7. **Xie, C. et al. Effect of pneumothorax on pleurodesis induced with talc in rabbits. Chest 1998;114(4):1143-6.**

Thirty rabbits received 400 mg/kg talc slurry by intrapleural injection. Second group (30 animals) received an intrapleural injection of 400 mg/kg talc slurry and 10 mL of air (equivalent to 240 mL of air in a 60-kg person) after the talc. Ten animals in each group were killed 2, 14, and 28 days after instillation.

The degree of gross adhesion and microscopic fibrosis was similar in both groups. The volume of pleural fluid, pleural fluid glucose, protein, and cell count were also similar in both groups. The level of LDH in the pleural fluid was slightly higher (~1.3 fold) in the air group as compared to control group. These results suggest that the presence of a small amount of intrapleural air (~4 ml/kg) did not impair the production of a pleurodesis with talc slurry in normal rabbits.

8. **Vargas, FS. et al. Silver nitrate is superior to talc slurry in producing pleurodesis in rabbits. Chest 2000;118(3):808-13.**

Two groups of rabbits (10 animals/group, 2-2.5 kg body weight) received either 0.5% silver nitrate or 400 mg/kg talc intrapleurally in a total volume of 2 mL. The animals were killed on day 28 after injection and the evidence for pleurodesis, inflammation and fibrosis were examined.

The mean degree of pleurodesis (3.4±0.2 vs. 1.6±0.1), pleural fibrosis (3.3±0.3 vs. 1.8±0.1) and pleural collagen (3.0±0.2 vs. 1.6±0.2) were significantly higher in the rabbits that received silver nitrate than in those that received talc. In conclusion, silver nitrate was significantly better than talc in producing a pleurodesis.

9. **Vargas, FS. et al. Experimental pleurodesis in rabbits induced by silver nitrate or talc: 1-year follow-up. Chest 2001:119(5):1516-20**

Two groups of rabbits received either 2 mL of 0.5% silver nitrate or 400 mg/kg talc slurry in 2 mL intrapleurally. Ten animals in each group were killed at 1, 2, 4, 6, 8, 10, and 12 months after intrapleural injection. The degree of gross pleurodesis, pleural inflammation and fibrosis were examined.

Pleural macroscopic and microscopic changes observed from 1 to 12 months after intrapleural injection of silver nitrate or talc on both hemithoraces are shown on the next page.

Month	Treatment	Macroscopic adhesion		Pleural inflammation		Pleural fibrosis	
		R. hemithorax	L. hemithorax	R. hemithorax	L. hemithorax	R. hemithorax	L. hemithorax
1	Talc	1.7±0.1	0.0	1.6±0.3	0.0	1.9±0.1	0.0
	Silver nitrate	3.2±0.3*	0.2±0.2	2.0±0.3	1.2±0.2*	3.2±0.2*	1.6±0.3*
2	Talc	2.9±0.3	0.0	1.5±0.3	0.3±0.2	2.2±0.4	0.1±0.1
	Silver nitrate	3.1±0.2	0.2±0.2	0.8±0.1	0.2±0.1	3.2±0.2	0.4±0.2
4	Talc	2.1±0.2	0.0	0.9±0.1	0.0	2.3±0.3	0.2±0.1
	Silver nitrate	3.6±0.2*	0.3±0.2	0.8±0.2	0.3±0.2	3.3±0.3*	0.7±0.2
6	Talc	2.2±0.3	0.0	0.9±0.1	0.4±0.2	2.1±0.2	0.7±0.1
	Silver nitrate	3.1±0.2*	0.1±0.1	1.6±0.3	0.7±0.3	2.5±0.2	0.7±0.3
8	Talc	2.3±0.2	0.0	1.1±0.2	0.0	2.5±0.3	0.5±0.2
	Silver nitrate	3.1±0.2*	0.2±0.2	0.8±0.2	0.0	2.4±0.2	0.2±0.1
10	Talc	2.5±0.1	0.0	1.0±0.1	0.1±0.1	2.4±0.2	0.6±0.2
	Silver nitrate	3.5±0.2*	0.0	0.4±0.2*	0.0	1.9±0.2	0.1±0.1
12	Talc	2.4±0.2	0.0	1.0±0.1	0.1±0.1	1.9±0.2	0.4±0.2
	Silver nitrate	3.6±0.1*	0.3±0.2	1.4±0.3	0.5±0.2	2.1±0.2	0.6±0.2

Data are presented as mean±SEM * $p<0.05$ compared with talc on the same side at the same time.

The pleurodesis was distributed throughout the thorax in the rabbits that received silver nitrate. The pleurodesis was only in the ventral thorax in the rabbits that received talc slurry. It did not decrease during the 12-month observation period in either treatment group. The inflammation scores were similar in both groups at all observation times. The microscopic pleural fibrosis tended to decrease with time in silver nitrate but not in the talc slurry group. In conclusion, silver nitrate (2 mL of 0.5%) may be better in producing pleurodesis than talc slurry (400 mg/kg) in rabbits.

I PHARMACOLOGY CONCLUSION; Limited nonclinical pharmacology studies available from the published literature indicate that no safety concerns arise from the new method of administration. The mechanism through which talc slurry produces pleurodesis is not known.

II. SAFETY PHARMACOLOGY:

No additional data submitted

III. PHARMACOKINETICS/TOXICOKINETICS:

No additional data submitted

IV. GENERAL TOXICOLOGY:

No additional data submitted. See labeling with basis for findings below.

V. GENETIC TOXICOLOGY:

No additional data submitted

VI. CARCINOGENICITY:

No additional data submitted

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

No additional data submitted

VIII. SPECIAL TOXICOLOGY STUDIES:

No additional data submitted

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Please see NDA 20-587. Sponsor has not submitted any new data.

Recommendations: This NDA is approvable for Pharmacology/Toxicology.

Labeling with basis for findings:

Currently reads under **Carcinogenesis, Mutagenesis, Impairment of Fertility**, paragraph 3 (page 44, volume 1) Talc was not mutagenic to Salmonella typhimurium or Saccharomyces cerevisiae in host-mediated assays. It did not induce chromosomal aberration in cultured human cells or in rats in vivo or dominant lethal mutations in rats.

Full details of these assays are not available. The wording is apparently from IARC monograph on talc (Evaluation of the carcinogenic risk of chemicals to humans; Silica and Some Silicates; Volume 42, 1987). Therefore, the above paragraph should be **deleted** from the package insert.

Remaining Pharm/Tox portions of the proposed text of the labeling for the drug (page 40, volume 1) are acceptable. There are no other differences from previous label for years 2000 and 2001.

X. APPENDIX/ATTACHMENTS:
None

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/s/

Anwar Goheer
1/2/03 04:17:43 PM
PHARMACOLOGIST

John Leighton
1/2/03 04:22:20 PM
PHARMACOLOGIST