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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-388

Clinical Pharmacology and Biopharmaceutics Review

Office of Clinical Pharmacology and Biopharmaceutics

Submission / Date: NDA 21-388 / September 20, 2002

Brand name: Sterile Talc Powder

Generic name: Talc

Type of dosage form and strength(s): — g of powder in a single use glass bottle

Indication(s):
The Applicant seeks the following language: [

]

Applicant name:
Bryan Corporation

OCPB and ORM Division names:
Division of Pharmaceutical Evaluation 1 and Division of Oncologic Drug Products

OCPB Reviewer and Team Leader names:
Carl-Michael Staschen, M.D., Ph.D. and N.A.M. Rahman, Ph.D.

Type of Submission: New Drug Application (NME)

I. Executive Summary

The sponsor has submitted a literature based new drug application and is seeking FDA approval for marketing Sterile Talc Powder. Talc will be indicated for control of malignant effusions secondary to malignancies having spread to the pleural space. It is intended to be administered intrapleurally.

The sponsor is requesting a waiver of the requirement for evidence of *in-vivo* bioavailability for Sterile Talc Powder. The request is based on that

1. talc is administered directly into the pleural cavity,
2. measurement of blood levels of talc would be difficult if not impossible.

The OCPB reviewer agrees with this rationale.

A. Overall Recommendations

A waiver of the requirement for evidence of *in vivo* bioavailability is granted. The Clinical Pharmacology and Biopharmaceutics portion of this NDA is acceptable. No new risk management recommendations have resulted from this review.

B. Comments

None.

C. Labeling Comments

FDA proposes a revised version. OCPB recommends that the sponsor's text be modified. The statement [redacted] curently written after the "Clinical Pharmacology [redacted] " section will be moved to the DESCRIPTION section. From the proposed header [redacted] ' the part "Mechanism of Action" will move into the text and the header is reading only "CLINICAL PHARMACOLOGY". The sentence [redacted] " will be deleted. The following Table 1 compares the sponsor's submitted label revision as well as FDA's proposal.

Table 1. Package Insert	
Sponsor	**FDA**
Section **Clinical Pharmacology** [ ] [ ]	**Section** **CLINICAL PHARMACOLOGY**
Submitted	**Proposal**
The therapeutic action of talc instilled into the pleural cavity is believed to result from induction of an inflammatory reaction. This reaction promotes adherence of the visceral and parietal pleura, obliterating the pleural space and preventing reaccumulation of pleural fluid.[ ]	*Mechanism of action*: The therapeutic action of talc instilled into the pleural cavity is believed to result from induction of an inflammatory reaction. This reaction promotes adherence of the visceral and parietal pleura, obliterating the pleural space and preventing reaccumulation of pleural fluid.
[ ] The extent of systemic absorption of talc after intrapleural administration has not been adequately studied. Systemic exposure could be affected by the integrity of the pleural surface, and therefore could be increased if talc is administered immediately following lung resection or biopsy.	The extent of systemic absorption of talc after intrapleural administration has not been adequately studied. Systemic exposure could be affected by the integrity of the pleural surface, and therefore could be increased if talc is administered immediately following lung resection or biopsy.

FDA's reasoning for the revision is as follows: The deleted sentence addresses a clinical issue.

D. Phase 4 commitments

No Phase 4 commitments are recommended.

Recommendations: The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed this submission and has the labeling comments as described above. Please forward these comments to the sponsor.

/S/

Carl-Michael Staschen, M.D., Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: NDA 21,388
HFD-150/Division File
HFD-150/ SBradley, AFarrel, NScher
HFD-860/MMehta, CSahajwalla, ARahman, CStaschen
CDR Biopharm

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Appendices

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor has submitted a new NDA (letter date: September 20, 2002) to seek FDA approval for the "Sterile Talc Powder" product. The sponsor also requested an orphan designation for this drug, based on the fact that there are less than 200,000 U.S. patients to be treated with he sponsor' product.

The applicant has requested a waiver of the requirement for evidence of *in vivo* bioavailability. This petition is based on evidence in the literature that talc administered intrapleurally is generally confined to that area. In addition, the measurement of blood levels of talc would be "difficult if not impossible." A waiver was requested and granted when the FDA approved the applicant's NDA for aerosol talc (Sclerosol® Aerosol Talc Powder).

IV. Question Based Review

Background
Malignant pleural effusions are a significant cause of morbidity and usually associated with advanced lung, breast and ovarian cancer, and lymphoma. Talc has been used to control pleural effusions for over sixty years. The only intrapleural talc that is currently approved for marketing in the United States for this indication is Bryan Corporation's Sclerosol® aerosol talc (approved December 27, 1997 under NDA 20-587).

Sterile talc powder is a non-aerosol version of Bryan Corporation's Sclerosol® Sterile Aerosol talc. Sterile talc powder is supplied in a single use glass bottle containing — g of the same asbestos-free talc that is used for Sclerosol Aerosol Talc. The talc-filled bottle is sterilized by gamma radiation.

What is the physico-chemistry and formulation of talc ?
The composition of the talc is ≥ 95% talc as hydrated magnesium silicate. The empirical formula of talc is $Mg_3Si_4O_{10}(OH)_2$) with a molecular weight of 379.3 Dalton. Associated naturally occurring minerals include chlorite (magnesium and aluminum silicate), dolomite (calcium and magnesium carbonate), calcite (calcium carbonate) and quartz.
Sterile talc powder for human use is composed solely of Talc USP which is sterilized by gamma irradiation. Sterile talc powder is intended to be administered intrapleurally in the form of a slurry. The usual method of administration is via a chest tube. The talc is provided in the form of a single use 100 mL glass bottle containing a minimum of — g of sterile asbestos-free talc.

What is the dose and route of administration for talc ?
Sterile talc powder is mixed with sterile saline to make a slurry. The usual dose is a single — g dose delivered intrapleurally through a chest tube.

What is the mechanism of action, use and side effects of talc ?
The therapeutic action of talc is following its administration by intrapleural insufflation is due to its adsorption onto the pleura. The resulting inflammatory process adheres the parietal and visceral surfaces, effectively diminishing the pleural space and preventing re-accumulation of pleural fluid. Talc may be superior to other sclerosing agents since it is insoluble, has a prolonged effect and remains in situ for an extended period of time, possibly indefinitely. There are no reported serious side effects at doses between [redacted] g of talc. There have been rare cases of acute pneumonitis and adult respiratory distress syndrome following higher doses (10 g) of talc administration into the pleural space.

What are the pharmacokinetics/pharmacodynamics of talc?
There have been no clinical investigations performed by Bryan Corporation. All clinical data comes from published reports in the literature. Studies typically included in the development of new drugs have not been performed (i.e., drug disposition, pharmacokinetic/pharmacodynamic relationships, mass balance, possible interactions with concomitant therapy, etc.).

What is the proposed indication for talc ?
[redacted]

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Reviewer's comments:

1. The sponsor has requested a waiver of the requirements for evidence of *in-vivo* bioavailability for Sterile Talc Powder.

2. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient becomes available at the site of action. Since talc is administered in a manner that is well controlled in terms of the amount given and direct localization into the pleural cavity (i.e., site of action), bioavailability to the site of action is known.

3. One must assume that some proportion of the administered dose of talc gains access to the systemic circulation until this is ruled out by formal investigations. However, as the sponsor has pointed out, measurement of circulating levels of talc is not practical and probably not feasible.

Based on these points, the OCPB recommends a waiver for the requirement of evidence demonstrating the *in-vivo* bioavailability of Sterile Talc Powder be granted.

6 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carl-Michael Staschen
3/5/03 02:27:10 PM
PHARMACOLOGIST

Atiqur Rahman
3/7/03 02:12:01 PM
BIOPHARMACEUTICS