

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-587

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-587

Date of Submission: August 11, 1995

**Sclerosol (Sterile Aerosol Talc; Talc
Intrapleural administration, 4 grams
Bryan Corporation**

Review: Peter N. Zannikos, Ph.D.

Type of Submission: original NDA submission

SYNOPSIS

Pleural effusions are a significant cause of morbidity, frequently associated with metastatic cancer. Treatment of patients with effusions has included the use of talc as a pleural sclerosant. The therapeutic action of talc results from 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. Favorable characteristics of talc which support its use as a sclerosing agent include its poor solubility and prolonged effects. The latter is attributed to the fact that talc remains on pleural surfaces long after application.

Talc will be indicated for control of effusions secondary to malignancies having spread to the pleural space. It is intended to be administered intrapleurally. The recommended usual dosage is a single 4 - 8 gram dose. The talc will be packaged in a single-use disposable canister and sterilized by

The sponsor is requesting a waiver of the requirements for evidence of *in vivo* bioavailability for Sterile Aerosol Talc. This request is based on the following:

- i) talc is administered **directly** into the pleural cavity and is generally confined to that area.
- ii) measurement of blood levels of talc would be "difficult if not impossible."
- iii) numerous published reports indicate that talc has apparently been used successfully in the treatment of pleural effusions over the past sixty years without an approved marketing application for this indication.

The recommendation by the Division of Pharmaceutical Evaluation I is that a waiver is indicated for the requirement of evidence demonstrating the *in vivo* bioavailability of talc.

RECOMMENDATION:

NDA 20-587 has been reviewed by the Division of Pharmaceutical Evaluation I. The Division recommends that based on the following facts, a waiver is indicated for the requirement of evidence demonstrating the *in vivo* bioavailability of talc:

- i) Talc is directly instilled into the pleural cavity to control effusions and relieve symptoms through its action as a local sclerosing agent.
- ii) The general consensus by clinical investigators is that talc does not leave the pleural surfaces to enter any other body system and then only in small amounts.
- iii) Measurement of talc blood levels would be "difficult if not impossible."
- iv) Numerous published reports indicate that talc has apparently been used successfully in the treatment of pleural effusions over the past sixty years without an approved marketing application for this indication.

Labeling comments should be forwarded to the Sponsor.

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/S/

FT
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12-26-95

cc
 NDA: 20-587 (original)
 HFD-150: Catterson
 HFD-150: Martin
 HFD-860: Biopharm/Drug file
 HFD-860: Biopharm/Lesko
 HFD-860: Biopharm/Malinowski
 HFD-860: Biopharm/Mehta
 HFD-860: Biopharm/Rahman
 HFD-860: Biopharm/Zannikos
 HFD-150 Drug File (DIVISION FILE)

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BACKGROUND

Pleural effusions are a significant cause of morbidity, particularly in patients with advanced cancer. They are frequently associated with lung, breast and ovarian cancer, and lymphoma. The therapeutic action of talc 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.

Talc has been shown to be an effective pleurodesis agent as early as 1935. Dosages used in published clinical trials investigating the efficacy of talc for pleural effusions range from grams per treatment. A problem in the use of talc has been the assurance of sterility of the preparation. USP talc is supplied in a non-sterile condition and must be sterilized and packaged in each hospital. Further, preparation costs and quality control are at issue.

At the present time there are no approved marketing applications for talc in this indication. In an effort to encourage the submission of marketing applications for the use of talc in the treatment of pleural effusions, the Center for Drug Evaluation and Research sent a letter to approximately 20 companies (March 11, 1994) explaining that talc may qualify for handling as a drug under special procedures designed to facilitate the development of new therapies for critically ill patients. Bryan responded to CDER's letter and is seeking approval of a marketing application for sterile aerosol talc. The advantages this product offers include assured sterility and ease of delivery.

The sponsor is requesting a waiver of the requirements for evidence of *in vivo* bioavailability for Sterile Aerosol Talc. 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."

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PHYSICOCHEMICAL PROPERTIES:

Talc contains asbestos-free talc (hydrated magnesium silicate. $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$) and chlorite (magnesium and aluminum silicate) at a concentration of at least 95 %. Associated minerals include dolomite (< 3 %), calcite (trace elements only) and quartz (< 3 %).

Physical State:	solid, powder
Color:	white - light grey
pH:	suspension of 10 % in water, pH=9
Solubility:	in water < 0.1 %

is responsible for the manufacture, processing, packaging, and labeling of the drug substance, It is mined from the Trimouns quarry in
It is quarried, sorted, dried and powdered using mechanical processes only. No chemicals are introduced during these processes. must conform with the European Pharmacopeia, 2nd Edition. The following analytical procedures are used to control

FORMULATION:

Sterile Aerosol Talc will be supplied in a single-use spray canister for intrapleural administration by thoracoscopy. Each canister will contain 4.0 grams (asbestos-free and brucite-free). The spray canister delivers talc at the rate of 0.4 grams per second. Dichlorodifluoromethane (CFC-12) is the aerosol propellant, 26 grams per canister. The talc-filled canister is sterilized by and packaged in a sterile pack.

PHARMACOKINETICS/PHARMACODYNAMICS:

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.).

INDICATION:

Sterile Aerosol Talc will be indicated for the treatment of malignant pleural effusions secondary to malignancies having spread to the pleural space.

DOSAGE:

The recommended usual dosage is a single 4 - 8 gram dose delivered intrapleurally through a spray canister at a rate of 0.4 grams per second. The dose is to be individualized to each patient's needs.

COMMENTS (general):

1. Sterile Aerosol Talc is not intended to be absorbed into the systemic circulation. As a result, the extent of generalized systemic exposure following intrapleural administration in humans has not been assessed. Nonclinical studies have been performed which may provide some indication of the *in vivo* disposition of talc. One study examined talc pleurodesis in ten dogs. Animals were sacrificed after treatment and the localization of talc was directly observed. Talc grains did not appear to spread beyond visceral pleura. No spreading of talc and the reaction it entails was found in extrathoracic organs (Mathlouthi et al., *Rev Mal Resp*, 9, 1992). In contrast, rabbits administered talc slurry by intrapleural injection exhibited some talc outside the pleural space. Talc was found in mediastinal lymph nodes (4 of 23 animals), kidney (1 of 6) and spleen (4 of 10) sections (Kennedy et al., *Chest*, 107, 1995). The authors postulate that intrapleural talc moves into the parietal pleural lymphatics and eventually enters the systemic circulation. These studies used macroscopic and histologic examination of tissues. No estimation can be made with regards to the amount of talc found outside of the pleural cavity relative to the dose administered.
2. 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. The utility of measuring systemic levels (i.e., concentration in plasma) relates to safety issues. However, as the sponsor has pointed out, measurement of circulating levels of talc is not practical and probably not feasible.

According to the Code of Federal Regulations (CFR 320.22), FDA may waive a requirement for the submission of evidence of *in vivo* bioavailability if waiver is compatible with the protection of the public health. A review of the prior clinical experience with talc may provide information needed to address the issue of safety.

3. The sponsor has requested a waiver of the requirements for evidence of *in vivo* bioavailability for Sterile Aerosol Talc. This request is based on the following:
- i) Talc, instilled into the pleural cavity, controls the effusions and relieves symptoms through its action as a **local** sclerosing agent.
 - ii) Talc is insoluble in water. The general consensus by numerous clinical investigators is that talc does not leave the pleural surfaces to enter any other body system and then only in small amounts. The sponsor states that measurement of talc blood levels would be "difficult if not impossible."
 - iii) "Talc adhering to the pleural surfaces has been found on autopsy months after the treatment took place." Unfortunately, the sponsor has **not** provided any reference to this statement. Some evidence that talc remains adhered to the pleural surface for an extended period of time was provided in a 5-month follow-up radiograph of a patient treated with an iodized talc slurry preparation (Webb et al., *J Thorac Cardiovasc Surg*, 103, 1992). The prolonged effect of talc as compared to other sclerosing agents is also indicative that talc remains *in situ*.

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), this issue is not a major concern.

Based on these points, the Division recommends a waiver for the requirement of evidence demonstrating the *in vivo* bioavailability of talc be granted.

4. Based on comments found in the literature, talc is not considered to be systemically absorbed after instillation into the pleural cavity. Therefore, talc is not expected to interact with systemically administered drugs. However, the effectiveness of other sclerosing agents and the potential for drug-drug interaction in patients having undergone talc pleurodesis is not known and deserves careful consideration.

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APPENDIX:

- **Human Pharmacokinetic and Bioavailability Summary** (from Vol 1.1 of submission)
- **Proposed Text of the Labeling for Sterile Aerosol Talc**

2.6 HUMAN PHARMACOKINETIC AND BIOAVAILABILITY SUMMARY

The sponsor is requesting a waiver of the requirements for evidence of in vivo bioavailability for Sterile Aerosol Talc. This request is based on the evidence in the literature that talc, administered intrapleurally, only rarely leaves the pleural surfaces to enter any other body system and then only in small amounts. The measurement of blood levels of talc would be difficult if not impossible.

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