CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-388

Approved Labeling

PRESCRIBING INFORMATION **NDC 63256-200-04**

STERILE TALC POWDER

FDA FINAL VERSION

For Intrapleural Administration Only

DESCRIPTION

Sterile Talc Powder is a sclerosing agent intended for intrapleural administration supplied in a single use 100 mL brown glass bottle, sealed with a gray, 20 mm stopper and covered with a flip-off seal. Each bottle contains a minimum of 5.0 g of Talc *USP* (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of talc of controlled particle size. The composition of the talc is ≥ 95% talc as hydrated magnesium silicate. The empirical formula of talc is $Mg_3\ Si_4\ O_{10}\ (OH)_2$ with a molecular weight of 379.3. Associated naturally occurring minerals include chlorite (hydrated aluminum and magnesium silicate.), dolomite (calcium and magnesium carbonate), calcite (calcium carbonate) and quartz. Talc is practically insoluble in water and in dilute solutions of acids and alkali hydroxides. The finished product has been sterilized by gamma irradiation.

CLINICAL PHARMACOLOGY

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.

CLINICAL STUDIES

The data demonstrating safety and efficacy of talc slurry administered via chest tube for the treatment of patients with malignant pleural effusions are from the published medical literature. The following prospective, randomized studies were designed to evaluate the risk of recurrence of malignant pleural effusions in patient with a variety of solid tumors. The studies compared talc slurry, instilled into the pleural cavity via chest tube, versus a concurrent control. In all studies, after maximal drainage of the pleural effusion, the investigator administered talc slurry via the chest tube. Chest films documented response (defined as lack of recurrence of fluid for a period of time). Studies differed on the timing of the efficacy assessment. Zimmer *et al.* did not

specify the time required evaluations. Ong *et al.* specified the assessment at one month. Sorensen *et al.* specified the assessment at 3-4 months. The remaining studies assessed response at the completion of the follow-up period.

Randomized Controlled Trials Using Talc Slurry as a Sclerosing Agent

REFERENCE	TREATMENT	RESPONSE RATE EVALUABLE PTS* p value*	RESPONSE RATE ALL PTS* p value*
Sorensen *et al.* Eur J Respir Dis. 1984: 65(2):131-5	Talc Slurry 10g /250ml NS vs. Chest tube drainage alone	100% (9/9) vs. 58% (7/12) p=0.04	64% (9/14) vs. 41% (7/17) p=0.29
Noppen *et al.* Acta Clin Belg 1997; 52(4):258-62	Talc Slurry 5g/50-ml NS vs. Bleomycin 1mg/kg/50ml NS	79% (11/14) vs. 75% (9/12) p=1.00	79% (11/14) vs. 75% (9/12) p=1.00
Zimmer PW *et al.* Chest 1997; 112(2):430-434	Talc Slurry 5g/50 ml NS[c] vs. Bleomycin 60U/50 ml NS[c]	90% (17/19[b]) vs. 79% (11/14[b]) p=0.63	Not Given
Ong KC *et al.* Respirology 2000;5;99-103	Talc Slurry 5g/150ml NS[d] vs. Bleomycin 1U/kg/150 ml NS[d]	89% (16/18) vs. 70% (14/20) p=0.24	64% (16/25) vs. 56% (14/25) p=0.77
Yim AP *et al.* Ann Thorax Surg 1996; 62:1655-8	Talc Slurry 5g/50ml NS, lidocaine 2% 10 ml vs. Talc Insufflation 5g powder	90%(26/29) vs. 96% (27/28) p=0.61	90% (26/29) vs. 96% (27/28) p=0.61

* Two-sided p-value based on Fisher's exact test

[a] Patients were evaluable if chest x-rays were done to assess response per protocol.
The Sorensen study excluded patients if incomplete lung re-expansion was noted post drainage.

[b] Data per procedure (33 procedures in 29 evaluable patients, 3 patients with bilateral effusions).

[c] Plus lidocaine 1%, 20 ml.

[d] Plus lidocaine 1%, 10 ml.

In single-arm studies of malignant pleural effusions from the published literature, variously defined "success" rates using talc slurry pleurodesis ranged from 75% to 100%.

INDICATIONS AND USAGE

Sterile Talc Powder, administered intrapleurally via chest tube, is indicated as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients.

CONTRAINDICATIONS

None known

WARNINGS

None

PRECAUTIONS

1. **Future procedures:** The possibility of the future diagnostic and therapeutic procedures involving the hemithorax to be treated must be considered prior to administering Sterile Talc Powder. Sclerosis of the pleural space may preclude subsequent diagnostic procedures of the pleura on the treated side. Talc sclerosis may complicate or preclude future ipsilateral lung resective surgery, including pneumonectomy for transplantation purposes.

2. **Use in potentially curable disease:** Talc has no known antineoplastic activity and should not be used alone for potentially curable malignancies where systemic therapy would be more appropriate, e.g., a malignant effusion secondary to a potentially curable lymphoma.

3. **Pulmonary complications:** Acute Pneumonitis and Acute Respiratory Distress Syndrome (ARDS) have been reported in association with intrapleural talc administration. Three of the case reports of ARDS have occurred after treatment with a relatively large talc dose (10 g) administered via intrapleural chest tube instillation. One patient died one month post treatment and two patients recovered without further sequelae.

DRUG INTERACTIONS

It is not known whether the effectiveness of a second sclerosing agent after prior talc pleurodesis would be diminished by the absorptive properties of talc.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies on the carcinogenicity of talc have been performed using non-standard designs which prevent firm conclusions on its carcinogenicity. With single intraperitoneal administration to mice at 20 mg and observation for at least 6 months or 4 weekly doses administered intraperitoneally at 25 mg/dose to rats with observation for at least 84 weeks, tumor incidence was not increased. In these studies the talc

and its asbestos content were not characterized.

Genotoxicity was tested in cultures of rat pleural mesothelial cells (RPMC) as unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). None of the talc samples (which were asbestos-free) induced enhancement of UDS or SCEs in treated cultures. No information is available on impairment of fertility in animals by talc.

Pregnancy: Pregnancy Category B. An oral administration study has been performed in the rabbit at 900 mg/kg. Approximately 5 fold higher than a human dose on mg/m^2 basis, and has revealed no evidence of teratogenicity due to talc. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefit outweighs the risk.

Pediatric Use: The safety and efficacy of Sterile Talc Powder in pediatric patients have not been established.

Geriatric use: The estimated mean and median ages of patients treated with talc slurry from clinical studies (single-arm or randomized) were 60 and 62 years, respectively. No analyses to specifically evaluate the safety and efficacy in the geriatric population have been reported.

ADVERSE REACTIONS

Intrathoracic administration of talc slurry has been described in medical literature reports involving more than 2000 patients. Patients with malignant pleural effusions were treated with talc via poudrage or slurry. In general, with respect to reported adverse experiences, it is difficult to distinguish the effects of talc from the effects of the procedure(s) associated with its administration. The most often reported adverse experiences to intrapleurally-administered talc were fever and pain.

Infection: Complications reported include empyema.

Respiratory: Complications reported include hypoxemia, dyspnea, unilateral pulmonary edema, pneumonia, ARDS, brochopleural fistula, hemoptysis and pulmonary emboli.

Cardiovascular: Complications reported included tachycardia, myocardial infarction, hypotension, hypovolemia, and asystolic arrest

Delivery Procedure: Adverse reactions due to the delivery procedure and the chest tube may include: pain, infection at the site of thoracostomy or thoracoscopy, localized bleeding, and subcutaneous emphysema.

Chronic Toxicity: Since patients in clinical studies had a limited life expectancy, data on chronic toxicity are limited

OVERDOSAGE

No definite relationship between dose and toxicity has been established. Excessive talc may be partially removed with saline lavage.

DOSAGE AND ADMINISTRATION

Sterile Talc Powder should be administered after adequate drainage of the effusion. The success of the pleurodesis appears to be related to the completeness of the drainage of the pleural fluid, as well as the full re-expansion of the lung, both of which will promote symphysis of the pleural surfaces.

The recommended dose is 5 g, dissolved in 50 - 100 ml Sodium Chloride Injection, *USP*. Although the optimal dose for effective pleurodesis is unknown, 5 g was the dose most frequently reported in the published literature.

Talc Preparation

Prepare the talc slurry using aseptic technique in an appropriate laminar flow hood. Remove talc container from packaging. Remove protective flip-off seal.

Each brown bottle contains 5 g of Sterilized Talc Powder. To dispense the contents:

1. Using a 16 gauge needle attached to a 60-ml LuerLok syringe, measure and draw up 50 ml of Sodium Chloride Injection, *USP*. Vent the talc bottle using a needle. Slowing inject the 50 ml of Sodium Chloride Injection, *USP* into the bottle. For doses more than 5 g, repeat this procedure with a second bottle.

2. Swirl the bottle(s) to disperse the talc powder and continue swirling to avoid settling of the talc in the slurry. Each bottle will contain 5 g Sterile Talc Powder dispersed in 50 ml of Sodium Chloride Injection, *USP*.

3. Divide the content of each bottle into two 60 ml irrigation syringes by withdrawing 25 ml of the slurry into each syringe with continuous swirling. QS each syringe with Sodium Chloride Injection, *USP* to a total volume of 50 ml in each syringe. Draw air into each syringe to the 60 ml mark to serve as a headspace for mixing prior to administration.

4. When appropriately labeled, each syringe contains 2.5 g of Sterile Talc in 50 ml of Sodium Chloride Injection, *USP* with an air headspace of 10 ml. Once the slurry has been made, use within 12 hours or discard and prepare fresh slurry. Label the syringes appropriately noting the expiration date and time, with the statement "For Pleurodesis Only – NOT FOR IV ADMINISTRATION," the identity of the patient intended to receive this material and a

cautionary statement to SHAKE WELL before use.

5. Prior to administration, completely and continuously agitate the syringes to evenly redisperse the talc and avoid settlement. Immediately prior to administration, vent the 10 ml air headspace from each syringe.

6. Attach the adapter and place a syringe tip on the adapter. Maintain continuous agitation of the syringes.

NOTICE: Shake well before installation. Each 25 ml of prepared slurry in the syringe contains 1.25 g of talc. NOT FOR IV ADMINISTRATION.

Administration

Administer the talc slurry through the chest tube by gently applying pressure to syringe plunger and empty the contents of the syringe into the chest cavity. After application, discard the empty syringe according to general hospital procedures. After the talc slurry has been administered through the chest tube into the pleural cavity, the chest tube may be flushed with 10- 25 ml sodium chloride solution to ensure that the complete dose of talc is delivered.

Following introduction of the talc slurry, the chest drainage tube is clamped, and the patient is asked to move, at 20 to 30 minute intervals, from supine to alternating decubitus positions, so that over a period of about 2 hours the talc is distributed within the chest cavity. Recent evidence suggests that this step may not be necessary.

At the end of this period, the chest drainage tube is unclamped, and the excess saline is removed by the routine continual external suction on the tube.

HOW SUPPLIED

NDC 63256-200-04 Sterile Talc Powder is supplied in a 100 ml brown glass bottle containing 5 g of talc. The sterile bottle is closed with a gray stopper and covered with a flip-off seal.

Storage: Store at Room Temperature (18-25°C). Protect against sunlight.

DISTRIBUTED BY: Bryan Corporation. Woburn, MA 01801

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