CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205555Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	5/1/2017
From	Amna Ibrahim MD
Subject	Division Director Summary Review
NDA/BLA #	205555
Applicant	Nova tech S.A., Boston Medical Products Inc.
Date of Submission	04/15/2016
PDUFA Goal Date	05/15/2017
Proprietary Name / Non-Proprietary Name	Steritalc®/talc
Dosage Form(s) / Strength(s)	Powder provided in strengths of: 2 grams, in a 50 mL single-dose vial 4 grams, in a 50 mL single-dose vial 3 grams, in a 10 mL single-dose vial for use with Novatech SA's NOVATECH® TALCAIR™
Applicant Proposed Indication(s)/Population(s)	Steritalc is indicated • to decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. • in adults to decrease the recurrence of (b) (4) pneumothorax (b) (4)
Action/Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nancy Scher
Pharmacology Toxicology Review	George Chang
OPQ Review	Anamitro Banerjee et al
Clinical Pharmacology Review	Xianhua Cao
OPDP	Nazia Fatima
CDTL Review	Laleh Amiri-Kordestani
OSE/DMEPA	Tingting Gao
Pulmonary Consult	Lydia Gilbert McClain
CDRH Consult	Jitendra Virani

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Background

Steritalc (sterile talc) powder, was submitted under section 505(b)(2) in 2013. However, a Refuse-to-File letter was issued in May 2013 because "The application is incomplete because it does not on its face contain information required under 21 CFR 314.50." There were forty six items describing deficiencies with respect to general content and format of the NDA, chemistry, manufacturing and controls (CMC) for both the drug and for device components to be copackaged with the drug, clinical pharmacology information, and clinical safety and efficacy information. The RTF letter also listed additional items describing issues related to the content and formatting of the proposed label.

This NDA was resubmitted on 04/15/2016, again under section 505(b)(2), for the indication described on the previous page. The reference products are the Listed Drugs (LDs) Bryan Corporation's Sclerosol® aerosol talc (NDA 020587, approved by FDA in 1997) and Sterile Talc Powder (talc) (NDA 021388, approved by FDA in 2003). Both Talc and Sclerosol are indicated to prevent/decrease the recurrence of malignant pleural effusion. The indication to decrease the recurrence of (b) (4) pneumothorax proposed by the Novatech is, however, a new one. Steritalc has been available on the European market as a medical device for more than 20 years.

As outlined in the pulmonary consult, talc has been used in the management of (b) (4) pneumothorax since the 1940's. The pleurodesis options to reduce recurrence of pneumothorax are either surgical (i.e. via mechanical abrasion of the pleura) or chemical (via the use of sclerosing agents). The decision to utilize a surgical approach vs. chemical abrasion is multifactorial and includes patient considerations, as well as patient preference, and the underlying condition. Talc is the most common agent used for chemical pleurodesis and has the best success rate compared to other agents used. There are no approved sclerosing agents for pleurodesis for pneumothorax but according to the reports in the literature talc is the most effective and is best tolerated (less pain) compared to other sclerosing agents. The most common complaint following talc pleurodesis was pain (chest pain at the operative site) which resolved over time and there were no complaints of persistent intercostal pain in patients that were followed up beyond a year or longer. While talc is not approved for pneumothorax, the same principle that governs the use of talc in malignant pleural effusions is applicable to the condition of recurrent (b) (4) pneumothorax in that the goal is to achieve symphysis of the parietal and visceral pleura (pleurodesis) to prevent recurrence.

According to the label of the approved LD, Sterile Talc, talc instilled into the pleural cavity is thought to result in an inflammatory reaction. This reaction can promote adherence of the visceral and parietal pleura, which may prevent reaccumulation of pleural fluid. The recommended labeled dose for Steritalc for malignant pleural effusion is 2 to 5 grams and for pneumothorax is 2 grams, administered intrapleurally. The cumulative dose should be capped at 10 grams for safety reasons.

The clinical section for Steritalc is based on literature, as was the case for the LD. An important difference between Steritalc and the LDs is that the particle size for the former is graded to remove the smaller particles. The published literature appears to support a better toxicity profile for Steritalc compared to the non-graded LDs.

There were several serious issues with this application that included facilities inspections, microbiology issues, and lead content issues. Due to information provided by the Applicant on January 6, 2017, the goal date was extended by three months. Particularly due to the improved safety profile of Steritalc, the Agency kept close communication with Novatech to iron out issues proactively and expeditiously. All of the deficiencies were resolved.

The NDA will be approved for the following indications:

- To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion
- In adults to decrease the recurrence of pneumothorax

2. Product Quality

Steritalc is a white or off-white to gray powder which is graded to decrease the proportion of particles of a smaller size. It is provided as powder for intrapeural use in strengths of 2 grams, 3 grams, and 4 grams. The drug product is provided in single-use vials that are meant to be used immediately after preparation. Its chemical name is hydrated magnesium silicate.

The controls for asbestos were found satisfactory. The particle size of the drug substance is a critical quality attribute for this product, and is controlled (b) (4) (b) (4) Sufficient information was provided regarding the validation of the (b) (4) of the drug product by (b) (4). The subject vials and stoppers are depyrogenated (b) (4) respectively. All sterilization/ depyrogenation processes used in the manufacture of the drug product were adequately validated. The drug product conformed to the release specification for sterility and endotoxins. The issues regarding (b) (4) of the vials and the container closure integrity test were resolved. A biowaiver request was not deemed necessary.

The applicant indicated that they had (b) (4) . In addition, the facility informed FDA that they do not intend to manufacture the drug product in the future. This would generally have been a major issue for approval of a drug. To address this issue, the Office of Policy for Pharmaceutical Quality (OPPQ) was consulted. The conditions specific to this NDA were such that OPPQ advised that the application may be approvable even though the API site no longer intends to produce API for this application. All facilities associated with this NDA were recommended for approval.

I concur with the OPQ reviewers' conclusion that the CMC information provided in this application is acceptable.

3. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any nonclinical study data. Instead, the Applicant relied on nonclinical data from the labels of the LDs.

Apart from lead, (b) (4), elemental impurities comply with the levels indicated in the ICH Q3D. The risk assessment for these elements was evaluated by the pharm-tox reviewer, who found the proposed controls for these elements acceptable based on the dosage and duration of use. Given that there is no safe level of lead, especially in children, changes made to the package insert for Steritalc to communicate the potential risk of lead exposure and to limit the exposure in pregnant or lactating women and in children with pneumothorax. There does not appear to be a scientific cause for concern that warrants additional rodent carcinogenicity studies given the product characteristics, administration route and frequency of administration of Steritalc.

The Pharmacology/Toxicology team did not identify any issues that would preclude approval of this NDA.

4. Clinical Pharmacology

No clinical study and clinical pharmacology study have been submitted for this 505b2 application. The Applicant requested a waiver of the requirement for evidence of in-vivo bioavailability for Steritalc. Per the review, 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.” The extent of systemic absorption of talc after intrapleural administration has not been adequately studied.

The clinical pharmacology team stated that the NDA is approvable from a perspective.

5. Clinical Microbiology

NA

6. Clinical/Statistical-Efficacy

No clinical studies have been submitted by the Applicant for this 505b2 application. The Applicant has referenced the LDs and an updated literature review of adequate and well-controlled trials from the published literature with supportive single arm trials to demonstrate the efficacy of talc for the indication.

As noted in a comprehensive clinical review, Steritalc is marketed in more than 50 countries around the world and has been marketed in Europe since at least 1999 for pleurodesis. The published literature includes data on patients treated with Steritalc in Europe and elsewhere for (b) (4) patients with pneumothorax and malignant pleural effusion. Talc is an effective sclerosing agent.

There are published efficacy data for more than 250 patients treated with a talc product clearly identified as Steritalc for the malignant pleural effusion indication with a success rate of approximately 89% (range 73-91%).

For the pneumothorax indication, the applicant has provided adequate and well-controlled trials from the literature with supportive single arm trials to demonstrate the efficacy of talc for the indication. The applicant has also submitted several systematic treatment reviews from the literature which support efficacy. The reviewer also identified and reviewed published consensus guidelines for (b) (4) pneumothorax which recommend a procedure (surgical or chemical) after the second occurrence (b) (4). Pleurodesis with talc by poudrage or slurry are both effective options to decrease recurrence of pneumothorax.

The reviewer notes that for the malignant pleural effusion indication, the LD Bryan Sclerosol is labeled at a dose of 4-8 g for poudrage and the LD Sterile Talc Powder is labeled at a dose of 5 g for use as a slurry administered via chest tube. For malignant pleural effusion, Novatech Steritalc proposes dosing at 2-5 g either by poudrage or slurry, and this appears to be supported by the literature. For the pneumothorax indication, the proposed dose is (b) (4) 2 g. The dose supported in the published literature for the pneumothorax indication is 2 g. There are difference in particle size distribution (PSD) between Steritalc and the RLDs, with Steritalc having a lower percent of small particles. Based on literature review, the difference in PSD appears to favor Steritalc, with implications for safety.

The safety and efficacy is based on published literature studies of clinical trials involving talc slurry and talc poudrage in the (b) (4) of malignant pleural effusion and pneumothorax. Some of the studies provided specifically use Steritalc, while for others the source of talc is unknown. There are data from the literature for more than 500 patients treated with Steritalc for pneumothorax, some in conjunction with surgical procedures, with successful pleurodesis rates of 97-100%; and for more than 500 patients treated with Steritalc for pneumothorax, some in conjunction with surgical procedures, with successful pleurodesis rates of 97-100%.

7. Safety

The clinical reviewer states that Adult Respiratory Distress Syndrome (ARDS) has been reported in the literature with talc, and in the FDA Adverse Event Reporting System (FAERS) for the approved Bryan products in patients with malignant pleural effusion. The literature suggests an association of ARDS with the administration of higher doses of talc such as 10 g. The literature also suggests that acute pneumonitis/ARDS may be associated with talc products with smaller median particle size, due to systemic absorption of talc. Long-term studies have shown good preservation of pulmonary function many years after talc pleurodesis for pneumothorax. It has been suggested that conducting mechanical abrasion of

the pleura and/or biopsy at the time of talc instillation may also facilitate absorption of talc particles into the circulation by disrupting pleural capillaries. Trauma to pleural surfaces prior to talc pleurodesis could also facilitate systemic absorption of talc.

As noted by the CDTL, The most common adverse events (AEs) associated with talc pleurodesis are short-term pain and post-procedure fever. Empyema and local infection are infrequent, the latter more likely associated with indwelling tube thoracostomy required for administration of slurry. Some references suggest that empyema was related to variable practices for sterilizing talc, especially when unregulated, compounded talc was in common use. Other uncommon adverse reactions include dyspnea, arrhythmia, empyema, pneumonitis and acute respiratory distress syndrome (ARDS). Procedure related adverse reactions such as bleeding, hemothorax, wound infections, atelectasis and pneumonia may occur. As noted above, the difference in PSD appears to favor Steritalc, with implications for safety. The incidence of ARDS with talc pleurodesis is estimated to be approximately 1%. From the absence of reports of ARDS in many large trials, the current incidence appears to be lower than 1%. Multiple authors state that ARDS is associated with talc products with a larger proportion of smaller particles, due to the greater potential for systemic absorption. These authors suggest improved safety for graded talc such as the Novatech product, from which smaller particles are removed, and emphasize that reports of ARDS predominate from US and UK, where mixed talc is used. The data are inconclusive, but there is thought to be an association between the development of ARDS and use of higher doses of talc ≥10 grams.

If asbestos-free talc is used for pleurodesis, carcinogenicity is not a serious concern. Several long-term follow-up studies have shown good preservation of pulmonary function many years after talc pleurodesis for pneumothorax. In a study, 22-35 years after treatment with talc for PSP, no patients reported mesothelioma.

8. Advisory Committee Meeting

None

9. Pediatrics

Both the indications have been granted an orphan designation. The submission of a pediatric assessment or a waiver is not required for this application.

10. Other Relevant Regulatory Issues

- DSI Audits: not performed
- Financial Disclosure: no clinical studies were submitted
- Other consults- Suggestions from OPDP, DMEPA, and CDRH were discussed and were accepted as appropriate

- Pulmonary consult: The consultant agreed that there is sufficient information from the literature to evaluate benefit vs. risk for talc for the pneumothorax indication. Talc pleurodesis has been shown to be efficacious and safe with a success rate of ~ 95% in multiple large observational case series and has been used for decades.

There are no other unresolved relevant regulatory issues

11. Labeling

The Steritalc label is based on information provided in the NDA, labels of the two LDs and literature review. (b) (4) pneumothorax is a new indication to the Steritalc label. Other changes have also been made when compared to the label of the LDs. A recommendation for capping the cumulative dose at 10 grams is given, based on safety concerns. Given concerns about the lead content in the pediatric population and pregnant or lactating women, a Warning and Precaution subsection, a contraindication in pregnancy and additional information in 'Use in specific populations' section has been added. Description includes information regarding the grading to decrease the proportion of smaller size. The Clinical Studies section provides an overview from literature review pertaining to the two indications.

Other recommendations from consulted disciplines were discussed and added as appropriate.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Steritalc powder, was submitted under section 505(b)(2) for the proposed indications of (b) (4) of patients with malignant pleural effusion and pneumothorax (b) (4) (b) (4). Steritalc has been in use in Europe since 1999 and a substantial amount of literature supports the efficacy and suggests a better safety profile when compared to the approved LDs.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No REMS are required

- Recommendation for other Postmarketing Requirements and Commitments

No PMRs or PMCs are required

NDA 205555
Steritalc

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/s/

AMNA IBRAHIM
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