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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 26, 2017
From	Laleh Amiri-Kordestani, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205,555
NDA Type	505(b)(2)
Reference NDA	NDA 20,587 (Bryan) NDA 21,388 (Bryan)
Applicant	Novatech S.A.
Date of Submission	April 14, 2016
PDUFA Goal Date	May 14, 2017
Proprietary Name / Non-Proprietary Name	Talc powder/ STERITALC®
Dosage form(s) / Strength(s)	Powder / 2, 3, and 4 g, single-dose vial
Applicant Proposed Indication(s)/Population(s)	Steritalc is a sclerosing agent indicated: (b) (4) [redacted]
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	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 pneumothorax.

Discipline and Consultants	Reviewer	Team Lead
RPM	Elleni Alebachew	Christy Cottrell
Clinical	Nancy Scher	Laleh Amiri-Kordestani
Non-Clinical	George Chang	Todd Palmby
Clin/pharm	Xianhua Cao	Qi Liu
Product Quality – Branch Chief	Anamitro Banerjee	
Product Quality - DP	Nina Ni	
Product Quality - DS	Hari Sarker	
Product Quality - Process	Peter Guerrieri	
Product Quality - Facility	Marion Michaelis	
Biopharmaceutics	Gerlie Gieser	Okpo Eradiri
Microbiology	Yarery Smith,	John Metcalfe
Laboratory (OTR)	Akhtar Siddiqui	
RBPM	Kristine Leahy	
OPPQ	Brian Hasselbalch	
OSE RPM	Frances Fahnbulleh	
CDRH	Jitendra Virani	
Division of Pulmonary, Allergy & Rheumatology Products	Dr. Lydia Gilbert-McClain	

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This New Drug Application, NDA 205,555 for Steritalc® was submitted by Novatech S.A. under the provisions of section 505(b)(2) of the Federal, Food, Drug, and Cosmetic Act. The application is a resubmission following issuance of a Refuse to File (RTF) Letter on May 3, 2013. FDA cited 67 deficiencies. Some of the deficiencies include unsatisfactory organization and incompleteness of the application, illegible information, incomplete translation to English, inaccurate description of the proposed Reference Listed Drugs (RLDs), incomplete specifications for drug substance (DS), no documentation of bioequivalence of active ingredient to a reference drug or request for a waiver.

This application relies on the published litreture and FDA's previous findings of safety and efficacy for two listed drugs (Bryan Corporation products), Sclerosol® (NDA 20,587), approved in 1997, and Sterile Talc Powder (NDA 21,388), approved in 2003, for (b) (4) malignant pleural effusion (MPE). Sclerosol® is administered intrapleurally as an aerosol. Per Sclerosol® Intrapleural Aerosol (sterile talc powder) prescribing information, the usual dosage of it is a single 4-8 g delivered intrapleurally from the spray canister (1-2 cans), which delivers talc at a rate of 1.2 g per second. The recommended dose for Sterile Talc Powder is 5 g, suspended in 50 ml to 100 ml 0.9% Sodium Chloride Injection, USP. Sterile Talc Powder is administered as an aqueous slurry into a thoracostomy tube. Both products were 505(b)(2) applications, referencing the published literature, and Sterile Talc Powder also referenced Sclerosol for safety and efficacy. No clinical trials were conducted for the Bryan applications, nor were any trials conducted by Novatech for Steritalc®.

Therapeutic pleurodesis is commonly used to prevent recurrence of symptomatic malignant pleural effusions for cancers not responsive to systemic therapies and to treat recurrent or complicated pneumothorax. Pleurodesis may be achieved by surgical abrasion or by the instillation of a sclerosing agent such as talc into the pleural cavity to promote adherence of the visceral pleura to the parietal pleura.

Steritalc® is supplied as 2, 3, and 4 grams white or off-white to light gray, asbestos-free, sterile powder. It contains particle size-controlled talc, graded to decrease the proportion of smaller particles, compared with the current US-approved talc products, which are considered "mixed" talc. Steritalc® is marketed in more than 50 countries around the world and has been marketed in Europe since at least 1999 for pleurodesis. It is approved as a medical device in Europe and many countries throughout the world. Korea is the only country in which Steritalc is approved as a pharmaceutical (Nov 16, 2015). The data demonstrating safety and efficacy of talc in the (b) (4) malignant pleural effusions are derived from the published medical literature. In these studies, greater than 1000 patients with malignant pleural effusions have been reported to have had successful pleurodesis with talc, administered either by poudrage or as a slurry via chest tube. There are published efficacy data for more than 200 patients treated with STERITALC® for malignant pleural effusion. There are published efficacy data for more than 500 patients treated with STERITALC® for pneumothorax.

Recommended Regulatory Action: Approval

2. Introduction and Regulatory History

Therapeutic pleurodesis is commonly used to prevent recurrence of symptomatic malignant pleural effusions for cancers not responsive to systemic therapies and to treat recurrent or complicated pneumothorax. Pleurodesis may be achieved by surgical abrasion or by the instillation of a sclerosing agent into the pleural cavity to promote adherence of the visceral to the parietal pleura. Talc is a sclerosing agent, and instilling talc into pleural cavity leads to an inflammatory reaction promoting adherence of visceral and parietal pleura.

- Malignant pleural effusion (MPE) is a common cause of morbidity in patients with advanced cancer. Symptoms include progressive dyspnea, cough, and chest pain. Effusion is caused by direct pleural tumor invasion. The most common primary sites are lung cancer and breast cancer. MPE has been estimated to affect at least 150,000 people each year in the US (Clive 2016). Bethune (1935) introduced thoracoscopic talc poudrage in 1935 as a method to induce pleural adhesions to facilitate lobectomy. In 1958, Chambers reported the use of talc slurry administered by a chest tube to treat MPE in 1958. Talc powder is frequently administered intraoperatively by open surgical or thoracoscopic insufflation. Talc may also be administered bedside, following drainage of pleural fluid, as an aqueous slurry through a percutaneously placed chest tube,. Compounded US Pharmacopeia talcs were used in the US prior to the approval of Bryan Steritalc in 1997 (administered by aerosol during open thoracotomy or by thoracoscopy) and Bryan Sterile Talc Powder in 2003 (administered as aqueous slurry by chest tube).

- Pneumothorax is the presence of air in the pleural space with secondary lung collapse. The spectrum of severity may vary between asymptomatic and hemodynamically compromised. Pneumothorax may be "spontaneous," with no antecedent event or secondary to trauma. Since recurrences of spontaneous pneumothorax progressively increase after a second or third episode (How 2013), management of recurrent pneumothorax often includes pleurodesis after drainage. Both surgical and chemical methods have been used.

Steritalc will be supplied in 3 presentations, all containing only (b) (4), asbestos-free, USP grade talc powder, without excipients:

- Steritalc (b) (4) (2 g/vial)
- Steritalc (b) (4) (4 g/vial)
- Steritalc (b) (4) 3 (3 (b) (4) g/vial).

Steritalc (b) (4) and (b) (4) can be used as a suspension (slurry in saline solution) or as poudrage. Steritalc (b) (4) is intended to be used for the administration of talc poudrage in combination with Novatech's pulverization kit, Novatech Talcair device. The device is a powder blower comprised of an insufflation cannula, and insufflation bulb and connecting pieces, to attach the device to a vial.

The proposed doses of Steritalc for the indications are:

- Malignant pleural effusion (MPE), 2-5 grams intrapleurally
- Pneumothorax (PNX), (b) (4)2 grams intrapleurally

For both indications, the applicant proposes "discretion" in dosing to the physician, "but a cumulative dosage of 10 g should not be exceeded."

The following table summarizes important pre-submission regulatory activity for this application.

Date	Meeting or Event
December 8, 1997	Orphan Drug Status granted for malignant pleural effusion (MPE) (#97-1067)
	Orphan Drug Status granted for pneumothorax (#97-1092)
February 17, 2009	Type B pre-IND (#104,068)/pre-NDA meeting between Novatech and FDA/Division of Drug Oncology Products (DDOP) regarding Steritalc (sterile talc powder). FDA responded that an NDA submission under section 505(b)(2) of the Act, referencing published literature, might be acceptable. FDA responded to Novatech's questions about user fees and establishment fees.
March 1, 2013	NDA submitted to FDA/Division of Oncology Products 2
May 3, 2013	DOP2 issued a Refuse to File Letter
June 27, 2013	Type A meeting between Novatech and DOP2 to discuss RTF Letter
March 31, 2016	Talcair powder blower for talc insufflation FDA cleared (K151832) for the MPE indication
April 15, 2016	Novatech resubmited NDA to FDA/Division of Oncology Products 1
June 23, 2016	Application was filed
March 13, 2017	Talcair powder blower for talc insufflation FDA cleared (K151832) for the pneumothorax indication

3. Product Quality

Source: CMC Review

Final CMC Team Recommendation: Approval.

Drug Substance and Product: (*Drs.* Hari Sarker, Nina Ni and Anamitro Banerjee*)*

The proposed product, STERITALC®, is composed of (b) (4) asbestos free sterile talc powder ($Mg_3Si_4O_{10}(OH)_2$); hydrated magnesium silicate. In this NDA, the Drug Substance (DS) (Talc, also termed as (b) (4) will be sourced from (b) (4) . No chemical or biological additives are introduced during the

production of STERITALC®. According to Ph. Eur. and USP, talc may contain variable amounts of associated minerals among which chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate) and dolomite (calcium and magnesium carbonate). The finished drug product (DP) is a powder with strengths, 2g, 3g and 4g also designated as Steritalc (b) (4) Steritalc (b) (4) and Steritalc (b) (4) respectively. It is noted that STERITALC® is a sterile DP with controlled particle size distribution.

Per CMC reviewer's comment, the DS is a complex inorganic compound. The finished DP is (b) (4) The composition slightly varies based on sources.

Particle Size Distribution: (*Drs. Akhtar Siddiqui* and Anamitro Banerjee)

This product is graded to remove particles less than (b) (4) microns. Steritalc has a particle size distribution specification to control smaller particles (b) (4) Per Literature report and testing by the FDA laboratories, this product has fewer particles (b) (4) .

Biopharmaceutics: From a Biopharmaceutics perspective (Drs. Gerlie Gieser and Okpo Eradiri), NDA 205,555 for STERITALC® is recommended for APPROVAL.

The Applicant requested an *in vivo* bioavailability biowaiver in connection with the literature-based 505(b)(2) NDA of STERITALC® (talc powder for intrapleural use). This biowaiver request is not deemed necessary because the bioavailability of locally (intrapleurally) administered talc for pleurodesis is self-evident and can be established consistent with 21 CFR 320.24(b)(6). Additionally, adequate bridging was established to the drug products evaluated in some literature studies because either STERITALC® itself or comparable sterile talc products were evaluated for efficacy and/or safety in (b) (4) malignant pleural effusions and/or (b) (4) pneumothorax.

Environmental assessment: Per reviewers' assessment (Dr. Raanan Bloom) the applicant's claim for categorical exclusion is acceptable.

EA reviewer found the claim of categorical exclusion is acceptable based on the followings:

- Talc is a naturally occurring mineral with many uses;
- Treatment procedures minimize environmental releases.

A separate EA review was not required.

Facility reviews/inspection: Per facility reviewers' assessment (Drs. Marion Michaelis and Zhihao Peter Qiu), all facilities associated with this NDA are recommended for approval.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Review (Drs. George Ching-Jey Chang, Ph.D and Todd Palmby)

Final Pharmacology/Toxicology Team Recommendations: Approval

This application relies on FDA's previous findings of safety and efficacy for the listed drug. No nonclinical pharmacology/toxicology data were submitted in the Application.

Talc is a mined product that is produced and it contains various levels of elemental impurities as part of the particles of talc,which are not introduced from any part of the manufacturing process, and (b) (4) t (b) (4) Upon review of the elemental impurity risk assessment, levels of lead, (b) (4) in STERITALC Talc Powder drug product were found to result in exposures exceeding the permitted daily exposures (PDEs) specified in the ICH Q3D guideline. The Pharmacology/Toxicology team, the CMC team and the Applicant agreed to an acceptable specification for lead in the drug product.

I agree with pharm/tox review team that there is no safe level of lead, especially in children, the package insert of STERITALC was modified to communicate the potential risk of lead exposure and to limit the exposure in pregnant or lactating women and in children with pneumothorax.

Levels of (b) (4) also exceeded their respective PDEs specified in ICH Q3D for parenteral drugs. The Applicant proposed to test for the levels of these four elemental impurities yearly.

I agree with Pharmacology/Toxicology review team that given the intrapleural administration route and the single or maximum of two administrations for a maximum total of 10 g of talc and the seriousness of the indication, levels of (b) (4) are justified and do not warrant additional labeling changes.

The potential risk for carcinogenesis by STERITALC was also reviewed by Pharmacology/ Toxicology team. A comprehensive literature search was conducted. Only one nonclinical publication relevant to talc carcinogenicitywas found that suggested that talc was not carcinogenic for female genital system in a pilot long-term study in rats.

I agree with Pharmacology/Toxicology review team that since STERITALC is to be administered as a single dose, or a maximum of two doses and according to the ICH S1A guideline, "The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals," rodent carcinogenicity studies are not generally warranted for pharmaceuticals administered for less than 6 months on a continual basis; 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.

5. Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Xianhua Cao and Qi Liu)

Final Clinical Pharmacology Team Recommendations: Approval

No clinical and clinical pharmacology studies were conducted by the Applicant for this application. The reference products are indicated to prevent/decrease the recurrence of malignant pleural effusion. The proposed indications for Steritalc® include (b) (4) malignant pleural effusion at 2 to 5 grams and pneumothorax at (b) (4) 2 grams. The proposed drug product has different strengths compared to the referenced products.The Applicant is relying on the published literature studies involving talc slurry and talc poudrage in the (b) (4) malignant pleural effusion and pneumothorax, as well as the Agency's findings of safety and effectiveness for the approved reference products Scleorosol® and Talc, to support the approval of their product.

The Applicant is requesting a waiver of the requirement for evidence of *in vivo* bioavailability for Steritalc®. This petition was 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 reviewer concluded in the review that as the reference product Sterile Talc Powder (talc) (NDA 021388, approved in 2003) labeling was updated in 2014 and was included as reference for tentative approval, no clinical pharmacology related labeling changes were recommended. I concur with the reviewer.

6. Microbiology

Per the microbiology reviewer's assessment (Yarery Smith, Ph.D), there are no outstanding microbiology product quality issues that preclude approval.

The drug product is (b) (4) vials and stoppers are depyrogenated (b) (4) All sterilization/ depyrogenation processes used in the manufacture of the drug product have been adequately validated. The drug product conformed to the release specification for sterility and endotoxins.

7. Devices and Companion Diagnostic Issues

Source: CDRH reviewer *(Dr Jitendra Virani)*

At the time of the NDA submission, NOVATECH® TALCAIR™, was cleared only for one indication "Treatment of malignant pleural effusion by insufflation of medical grade talc following drainage of pleural fluid " (K151832).
And there was no device cleared in the US for the pneumothorax indication. Per Agency's request, Novatech submitted (K170030) on Jan. 3, 2017, to request clearance for their Talcair device for the pneumothorax indication, since the Talcair device was only cleared for talc poudrage for malignant pleural effusion. The Center for Devices and Radiological Health (CDRH) completed their review and issued a 510K clearance on March 13, 2017 for the pneumothorax indication.

8. Clinical: Efficacy and Safety Summary

Source: Clinical Review (Dr Nancy Scher)

Final Clinical Team Recommendations: Approval

The application references published literature and two Bryan Corporation products, Sclerosol® (NDA 20,857), approved in 1997, and Sterile Talc Powder (NDA 21,388), approved in 2003, for (b) (4) malignant pleural effusion (MPE). Both products were 505(b)(2) applications, referencing the published literature. No clinical trials were conducted for the Bryan applications, nor were any trials conducted by Novatech for Steritalc.

For MPE, the applicant has referenced the NDA clinical reviews for the 2 previously approved talc products. The applicant has also conducted an updated literature review to provide adequate and well-controlled trials from the published literature with supportive single arm trials to demonstrate the efficacy of talc for the indication. There are published efficacy data for more than 200 patients treated with a talc product clearly identified as Steritalc for the MPE indication, with a success rate of approximately 89% (range 73-91%).

For PNX, 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. There are data from the literature for more than 500 patients treated with Steritalc for PNX, some in conjunction with surgical procedures, with successful pleurodesis rates of 97-100%. The applicant has also submitted several systematic treatment reviews from the literature which support efficacy. FDA identified and reviewed published consensus guidelines for treatment of primary spontaneous PNX (PSP) from the European Respiratory Society (Tschopp 2015) and the American College of Chest Physicians (Baumann 2011). In general, the guidelines recommend a procedure (surgical or chemical) after the second occurrence of uncomplicated PSP or after the initial episode of secondary SP. Pleurodesis with talc by poudrage or slurry are both effective options to decrease recurrence of PNX.

For the MPE indication, the RLD Bryan Sclerosol is labeled at a dose of 4-8 g for poudrage and the RLD Sterile Talc Powder is labeled at a dose of 5 g for use as a slurry administered via chest tube. For MPE, Novatech Steritalc proposes dosing at 2-5 g either by poudrage or slurry,

and this appears to be supported by the literature. For the PNX indication, the proposed dose is (b) (4) 2 g.

I agree with clinical reviewer that labeled dose of 2-5 g for MPE, as proposed by the applicant, appears acceptable. However, the dose supported in the published literature for the PNX indication is 2 g.

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.

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 PNX. In the study by Lange (1988) of patients 22-35 years after treatment with talc for PSP, no patients had developed mesothelioma.

9. Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee.

10. Pediatrics

STERITALC® (Sterile Talc) was granted orphan drug designation for both indications, therefore submission of a pediatric assessment, or a waiver was not required for this application.

- Orphan Designation number - 97-1067 on 12-08-1997 for (b) (4) malignant pleural effusion, and
- Orphan Designation number - 97-1092 on 12-08-1997 for (b) (4) pneumothorax.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Summary of Significant Labeling Changes *(High level changes and not direct quotations)*		
Section	**Proposed Labeling**	**Approved Labeling** ***(As of April 21, 2017)***
1 Indications and Usage	STERITALC® is a sclerosing agent indicated: (b) (4)	STERITALC® is a sclerosing agent indicated: • To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. (**Error! Reference source not found.**) • In adults to decrease the recurrence of pneumothorax. (**Error! Reference source not found.**)
2 Dosage and Administration	• Pneumothorax: intrapleural (b) (4) 2 g (**Error! Reference source not found.**)	• Pneumothorax: The recommended dose is 2 grams administered intrapleurally. • Do not exceed a total cumulative dosage of 10 grams per procedure. (**Error! Reference source not found.**)
4 Contraindications	• None	• Pregnancy. (**Error! Reference source not found.**, 5.3, 8.1)
5 Warnings and Precautions	• Pneumonitis and Acute Respiratory Distress Syndrome (ARDS): Acute Pneumonitis and ARDS, including fatal cases, occur with intrapleural talc administration. (**Error! Reference source not found.**) • Interference with Future Procedures: Sclerosis of the pleural space may preclude or complicate subsequent	• Pneumonitis and Acute Respiratory Distress Syndrome (ARDS): Acute Pneumonitis and ARDS, , have been reported with intrapleural use of various talc products. . (**Error! Reference source not found.**) • Interference with Future Procedures: Sclerosis of the pleural space may preclude or complicate subsequent ipsilateral surgery and diagnostic procedures. (**Error! Reference source not found.**)

	ipsilateral surgery and diagnostic procedures. (**Error! Reference source not found.**)	• Lead Content: STERITALC® contains lead as an impurity. May cause lead toxicity, especially in children. (5.3)
6 Adverse Reactions	Common adverse reactions observed with intrapleurally-administered talc are fever and pain. Other adverse reactions include dyspnea, arrhythmia, empyema, and acute respiratory distress syndrome.	Common adverse reactions observed with intrapleural use of various talc products are fever and pain. Other adverse reactions include dyspnea, arrhythmia, empyema, pneumonitis and acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions (5.1)]*. Procedure related adverse reactions such as bleeding, hemothorax, wound infections, atelectasis and pneumonia may occur.
8. Use in Specific Populations	**8.1 Pregnancy** (b) (4)	**8.1Pregnancy** *Risk Summary* STERITALC® is contraindicated for use in pregnant women because it contains lead, which can cause fetal harm and potential loss of pregnancy *[see Warnings and Precautions (5.3)]*. There are no human data on the use of STERITALC® in pregnant women. In an animal reproduction study, oral administration of talc in pregnant rabbits during organogenesis revealed no evidence of teratogenicity at dose up to approximately 5 times the human dose *[see Data]*. *Data* Animal Data In an embryo-fetal developmental toxicity study in rabbits, talc was administered to rabbits by oral gavage daily during the period of organogenesis at doses up to 900 mg/kg (approximately 5 times the human dose on a mg/m^2 basis). No significant dose-related toxicity was reported except at maternally toxic doses. In multiple animal studies,

	(approximately 5 times the human dose on a mg/m^2 basis). No significant dose-related toxicity was reported except at maternally toxic doses. In multiple animal studies, intrapleurally administered talc was not absorbed systemically. **8.2 Lactation** (b) (4) **8.4 Pediatric Use** Safety and effectiveness have not been established in pediatric patients.	intrapleurally administered talc was not absorbed systemically. **8.2Lactation** *Risk Summary* There is no information regarding the presence of talc in human milk, the effects on the breastfed infants, or the effects on milk production. STERITALC® contains lead, which is known to have adverse effects on health and development in neonates, infants and children *[see Warnings and Precautions (5.3)]*. Because of the potential for serious adverse reactions in breast-fed infants from lead content in STERITALC®, advise lactating women not to breastfeed during treatment with STERITALC® and for 5 months after the final dose. **8.3Females and Males of Reproductive Potential** *Contraception* STERITALC® contains lead, which can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 5 months following the final dose of STERITALC®. *Infertility* STERITALC® contains lead, which may impair fertility in males of reproductive potential *[see Warnings and Precautions (5.3)]*. **8.4Pediatric Use** Safety and effectiveness have not been established in pediatric patients.

		Lead is present in STERITALC® as an impurity *[see Warnings and Precautions (5.3)]*
11. Description	STERITALC® is a sclerosing agent for intrapleural administration. STERITALC® is white or off-white to light gray, asbestos-free talc powder of controlled particle size. The powder is ≥ 95% hydrated magnesium silicate [$Mg_3Si_4O_{10}(OH)_2$, molecular weight 379.3]; associated minerals include chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate). Talc is insoluble in water.	STERITALC® (talc) is a sclerosing agent for intrapleural administration. The molecular formula for talc is $Mg_3Si_4O_{10}(OH)_2$. The molecular weight is 379.3 g/mole. The chemical name of talc is hydrated magnesium silicate. The talc powder contains ≥ 95% of hydrated magnesium silicate; associated minerals include chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate). The talc elementary sheet is composed of a layer of magnesium-oxygen/hydroxyl octahedra, sandwiched between two layers of silicon-oxygen tetrahedra. Talc is insoluble in water. STERITALC® is supplied as 2 grams, 3 grams, and 4 grams white or off-white to light gray, asbestos-free, sterile powder. STERITALC contains particle size-controlled talc, graded to decrease the proportion of smaller particles.
13. Nonclinical Toxicology	**13.1 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	**13.1 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)

	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.	for 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.
14. Clinical Studies	(b) (4)	**14.1 Malignant Pleural Effusion** The data demonstrating safety and efficacy of talc in the treatment of malignant pleural effusions are derived from the published medical literature. In these studies, greater than 1000 patients with malignant pleural effusions have been reported (with varying degrees of detail and durations of response) to have had successful pleurodesis with talc, administered either by poudrage or as a slurry via chest tube. There are published efficacy data for more than 200 patients treated with STERITALC® for malignant pleural effusion, with a success rate of approximately 89% (range 73-91%). **14.2 Pneumothorax** The data demonstrating safety and efficacy of talc in the treatment of pneumothorax are derived from the published medical literature. There are published efficacy data for more than 500 patients treated with STERITALC® for pneumothorax, some in conjunction with surgical procedures, with successful pleurodesis rates of 97-100%.

13. Postmarketing Recommendations

Not applicable.

14. Recommended Comments to the Applicant

Not applicable.

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/s/

LALEH AMIRI KORDESTANI
04/26/2017