CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205555Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review

NDA/SDN	205555/SDN 10 \\CDSESUB1\EVSPROD\NDA205555\205555.enx
Brand Name	Steritalc®
Generic Name	Talc
Submission Date	4/14/2016
Submission Type	NDA, 505(b)(2), Resubmission after refusal to file.
Review Classification	Standard
PDUFA Goal Date	2/14/2017
Proposed Dosage Form /Strength	White or off-white to light gray sterile powder: 2, 3 and 4 grams in a single-dose glass vial.
Proposed Dosing Regimen	Intrapleural administration. A cumulative dosage of 10 g should not be exceeded. • For malignant pleural effusion: 2 to 5 grams; • For pneumothorax (b) (4) 2 grams;
Proposed Indication	1. Malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. 2. Pneumothorax
Listed Drug	Sterile Talc Powder (talc) and Sclerosol®
Applicant	Novatech S.A.
OCP reviewer	Xianhua (Walt) Cao, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 1 (DOP1)

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1 EXECUTIVE SUMMARY

This 505(b)(2) New Drug Application (NDA) submitted by Novatech S.A. is for a talc powder Steritalc® for intrapleural administration only. The reference products are Bryan Corporation's Scleorosol® aerosol talc (NDA 020587, approved by FDA in 1997) and Sterile Talc Powder (talc) (NDA 021388, approved by FDA in 2003). Both referenced products are talc sclerosing agents for intrapleural administration and 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. In addition, the proposed drug product has different strengths compared to the referenced products.

No clinical study and clinical pharmacology study are conducted by the applicant for this application. The applicant is relying on the published literature studies involving talc slurry and talc poudrage in (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®.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology V has reviewed the information contained in NDA 205555/SDN10.The NDA is approvable from a clinical pharmacology perspective.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

None.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The applicant has submitted a new NDA to seek FDA approval for a sterile talc powder product Steritalc® for (b) (4) malignant pleural effusion and pneumothorax. The applicant is relying on the published literature studies involving talc slurry and talc poudrage in (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 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." The extent of systemic absorption of talc after intrapleural administration has not been adequately studied.

Signatures:

Xianhua (Walt) Cao, Ph.D. Reviewer Division of Clinical Pharmacology V	Qi Liu, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: DDOP1: MO – Nancy Scher; MTL – Laleh Amiri Kordestani; RPM – Elleni Alebachew
DCPV: DDD –Brian Booth; DD – Atiqur Nam Rahman

2 QUESTION BASED REVIEW

For brevity, only QBR questions related to the current submissions are addressed below. Refer to the clinical pharmacology review for the reference products Bryan Corporation's Scleorosol® aerosol talc (NDA 020587, approved in 1997) and Sterile Talc Powder (Talc) (NDA 021388, approved in 2003).

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Steritalc® is composed of (b) (4) asbestos free sterile talc powder. Chemically talc is hydrated magnesium silicate, the molecular formula is $Mg_3Si_4O_{10}(OH)_2$ and the molecular weight is 379.3 g/mol. No chemical or biological additives are introduced during the production of Steritalc®. Only mechanical procedures are used. The drug products are provided as white or off-white to light gray sterile powder in a single-dose glass vial with the following strengths:

- STERITALC® (b) (4), talc in glass vial, 2 g
- STERITALC® (D) (4) talc in glass vial, 4 g
- STERITALC® (D) (4) talc in glass vial, 3 g; to be used with Novatech S.A.'s TALCAIR® pulverization kit.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

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 air or fluid. There are two proposed indications:

1. For (b) (4) malignant pleural effusion; to decrease the recurrence of malignant pleural effusion in symptomatic patients following maximal drainage of the pleural effusion. The recommended dose for this indication is 2 to 5 grams.
2. For (b) (4) pneumothorax. The recommended dose for this indication is (b) (4) 2 grams.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Steritalc® is a powder for intrapleural administration. When administering talc as slurry, it is recommended to use 10 mL of sterile isotonic saline solution (NaCl 0.9%, suitable for parenteral use) for each 1 g of talc. According to the physician's discretion, and in consideration of diagnosis and patient's condition, different dosages may be applied, but a cumulative dosage of 10 g should not be exceeded. The recommended dose for the proposed indications:

1. For (b) (4) malignant pleural effusion is 2 to 5 grams.
2. For (b) (4) pneumothorax is (b) (4) 2 grams.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the pharmacokinetics/pharmacodynamics of talc?

There have been no clinical investigations performed by Novatech S.A. All clinical data comes from published reports in the literature involving talc slurry and talc poudrage in (b) (4) malignant pleural effusion and pneumothorax, and the findings of safety and effectiveness for the approved reference products Bryan Corporation's Scleorosol® aerosol talc (NDA 020587, approved in 1997) and Sterile Talc Powder (talc) (NDA 021388, approved in 2003).

Clinical studies performed to evaluate human pharmacokinetics (PK) of intrapleural talc administration are not common, as talc is not believed to be significantly absorbed. To this day, the extent of systemic absorption of talc after intrapleural administration remains inadequately studied. The applicant has requested a waiver of the requirement for evidence of in-vivo bioavailability for Steritalc®, which is granted by the Biopharmaceutics review team.

3 DETAILED LABELING RECOMMENDATIONS

The reference product Sterile Talc Powder (talc) (NDA 021388, approved in 2003) labeling was updated in 2014 and is included as reference for tentative approval. No clinical pharmacology related labeling changes are recommended.

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

/s/

XIANHUA W CAO
01/11/2017

QI LIU
01/13/2017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205555

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission: NDA205555 is submitted under Section 505(b) (2), and is relying upon published literature, as well as the Agency's findings of safety and efficacy for both products: SCLEROSOL® (approved in 1997 under NDA 20587), and Sterile Talc Powder (approved in 2003 under NDA 21388). NDA 205555 was initially submitted to FDA on March 1, 2013. Following preliminary review, the NDA was issued a "Refusal to File" letter dated May 03, 2013. This is the resubmission to the RTF. \\CDSESUB1\EVSPROD\NDA205555\205555.enx

	Information		Information
NDA/BLA Number	205555 (SDN 10)	**Brand Name**	Steritalc®
OCP Division (I, II, III, IV, V)	OCP Division V	**Generic Name**	Talc
Medical Division	DOP1	**Drug Class**	
OCP Reviewer	Xianhua(Walt) Cao, Ph.D.	**Indication(s)**	1. For (b) (4) malignant pleural effusion. To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion. 2. For (b) (4) pneumothorax
OCP Team Leader	Qi Liu, Ph.D.	**Dosage Form**	White or off-white to light gray sterile powder in a single-dose glass vial; provided in the following strengths: (b) (4) 2 mg Strength STERITALC® vial (b) (4) for use as a slurry or poudrage (b) (4) 3 mg Strength (b) (4) (b) (4), to be used with Novatech S.A.'s TALCAIR® pulverization kit, for use as a poudrage (b) (4) 4 mg Strength – (b) (4) (b) (4) for use as a slurry or poudrage
Pharmacometrics Reviewer	N.A.	**Dosing Regimen**	Malignant Pleural Effusion: intrapleural 2 g to 5 g Pneumothorax: intrapleural (b) (4) 2 g
Date of Submission	4/14/2016	**Route of Administration**	intrapleural
Estimated Due Date of OCP Review		**Sponsor**	NovaTech
Medical Division Due Date		**Priority Classification**	Standard
PDUFA Due Date	2/14/2017		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			**All references**
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:		**0**	**0**	
Isozyme characterization:		**0**	**0**	
Blood/plasma ratio:		**0**	**0**	
Plasma protein binding:		**0**	**0**	
Pharmacokinetics (e.g., Phase I) -		**0**	**0**	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205555

Healthy Volunteers-				
single dose:		**0**	**0**	
multiple dose:		**0**	**0**	
Patients-				
single dose:		**0**	**0**	
multiple dose:		**0**	**0**	
Dose proportionality -				
fasting / non-fasting single dose:		**0**	**0**	
fasting / non-fasting multiple dose:		**0**	**0**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:		**0**	**0**	
In-vivo effects of primary drug:		**0**	**0**	
In-vitro:				
Subpopulation studies -				
ethnicity:		**0**	**0**	
gender:		**0**	**0**	
pediatrics:		**0**	**0**	
geriatrics:		**0**	**0**	
renal impairment:		**0**	**0**	
hepatic impairment:		**0**	**0**	
PD -				
Phase 2:		**0**	**0**	
Phase 3:		**0**	**0**	
PK/PD -				
Phase 1 and/or 2, proof of concept:		**0**	**0**	
Phase 3 clinical trial:		**0**	**0**	
Population Analyses -				
Data rich:		**0**	**0**	
Data sparse:		**0**	**0**	
II. Biopharmaceutics				
Absolute bioavailability		**0**	**0**	
Relative bioavailability -		**0**	**0**	
solution as reference:		**0**	**0**	
alternate formulation as reference:		**0**	**0**	
Bioequivalence studies -				
traditional design; single / multi dose:		**0**	**0**	
replicate design; single / multi dose:		**0**	**0**	
Food-drug interaction studies		**0**	**0**	
Bio-waiver request based on BCS		**0**	**0**	
BCS class		**0**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies		**0**	**0**	
Chronopharmacokinetics		**0**	**0**	
Pediatric development plan		**0**	**0**	
Literature References		**10**	**0**	**4 in vitro and 6 clinical studies for pharmacology of talc**
Total Number of Studies		**0**	**0**	

On **initial** review of the NDA/BLA application for filing:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205555

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			x	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			Waiver request submitted
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?			x	
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?			x	
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?			x	
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			Applicant has requested a waiver of the requirement for evidence of in vivo bioavailability
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA			x	

	meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205555

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?			x	
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 205555

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Xianhua (Walt) Cao Ph.D.	May 26, 2016
Reviewing Clinical Pharmacologist	Date
Qi Liu Ph.D.	May 26, 2016
Team Leader/Supervisor	Date

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

/s/

XIANHUA W CAO
06/03/2016

QI LIU
06/03/2016