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APPLICATION NUMBER:

207070Orig1s000

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH



PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: **NDA 207070**

Supporting document/s: **Sequences 0000**

Applicant's letter date: **September 14, 2014**

CDER stamp date: **May 2, 2014**

Product: **Spiriva[®] Respimat[®] (Tiotropium Bromide) Metered-Dose Inhaler**

Indication: **Asthma in patients 12 years and older**

Applicant: **Boehringer Ingelheim (BI) Pharmaceutical Inc.**

Review Division: **Division of Pulmonary, Allergy, and Rheumatology Products**

Reviewer: **Luqi Pei, Ph.D.**

Supervisor: **Marcie Wood, Ph.D.**

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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This review evaluates nonclinically the safety of NDA 207-070 which proposes to register Spiriva Respimat (tiotropium) for the treatment of asthma in patients 12 years of age and older. Spiriva Respimat is a product currently marketed for treatment of COPD in adults (NDA 21-936, approved on September 24, 2014). Nonclinical characterization of the product has been completed previously in NDAs 21-936 and 21-395 (Spiriva HandiHaler). The current submission contained no new, pivotal nonclinical studies for the safety evaluation of the current application.

The marketed Spiriva Respimat releases 2.5 mcg-tiotropium per actuation. The recommended human daily dose of Spiriva Respimat is two actuations once daily (i.e., 5 mcg-tiotropium/day). This NDA application introduced a new dosage form (1.25 mcg/actuation) and a lower clinical dose (2.5-mcg/day). The total daily dose proposed for asthma is lower than that approved for COPD. The lower clinical tiotropium dose does not affect the nonclinical safety evaluation and a full nonclinical review is unnecessary.

1.2 Brief Discussion of Nonclinical Findings

The product (Spiriva Respimat®, NDA 21-936) is an approved and currently marketed product. The labeling of Spiriva Respimat® states that tiotropium is non-genotoxic, non-carcinogenic and non-teratogenic in animals, although the drug was embryo/fetocidal when rats and rabbits were exposed to it during pregnancy.

1.3 Recommendations

1.3.1 Approvability

Approval of NDA 207070 is recommended from the nonclinical perspective. Spiriva Respimat is an approved and currently marketed product. No nonclinical data reveals any safety concern about the proposed clinical use of the product in asthmatics. The review recommends approval of the application from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

This review recommends the following text for Sections 8.1 and 13.1 of the Spiriva Respimat labeling. See Section 12 Labeling review for rationale and discussion about the labeling recommendations.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at

approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m² basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 40 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 430 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 4 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m² basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to 2 mcg/kg/day. These doses correspond to approximately 30, 40, and 0.5, times the recommended human daily inhalation dose (MRHDID) on a mcg/m² basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 78 mcg/kg/day or greater (approximately 40 times the MRHDID on a mcg/m² basis). No such effects were observed at 9 mg/kg/day (approximately 5 times the MRHDID on a mcg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1689 mcg/kg/day (approximately 910 times the MRHDID on a mcg/m² basis).

2 Drug Information

2.1 Drug

CAS Registry Number: 626247-18-6

Generic Name: Tiotropium

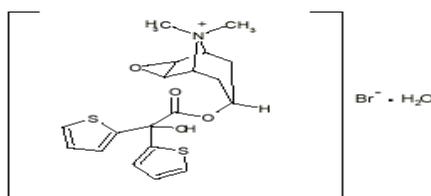
Code Name: Ba 679 BR

Chemical Name: (1 α , 2 β , 4 β , 5 α , 7 β)-[(hydroxydi-2-thienylacetyl)-9,9-dimethyl-3-oxa-9-azoniatrcyclo[3.3.1.0^{2,4}]nonane bromide monohydrate

Molecular Formula: C₁₉H₂₂NO₄S₂Br·H₂O

Molecular Weight: 490. (b) (4)

Structure:



Pharmacologic Class: Muscarinic cholinergic receptor antagonist

Clinical formulation: Aqueous inhalation aerosol solution delivered by a metered dose inhaler – Spiriva® Respimat®. The solution contains (b) (4) benzalkonium chloride and (b) (4) EDTA sodium as (b) (4). Each actuation delivers 1.25 µg tiotropium.

Route of administration: Oral inhalation

2.2 Relevant INDs, NDAs, and DMFs

See Table 1 for these applications.

Table 1: Tiotropium Applications

Appl. No.	Product	Indication	Status
IND 46,687	Tiotropium DPI	COPD	Active since 04/26/1996
IND 65,127	Tiotropium MDI	COPD/Asthma	Active since 06/28/2002
NDA 21-395	Spiriva HandiHaler	COPD	Approved on 01/30/2004
NDA 21-936	Spiriva Respimat	COPD	Approved on 09/24/2014
NDA 206756	Stiolto	COPD	Approved on 05/21/2015
NDA 207070	Spiriva Respimat	Asthma	In house

2.3 Drug Formulation

Spiriva® Respimat® is a metered-dose inhaler that delivers an aqueous tiotropium inhalation aerosol solution. The solution contains (b) (4) benzalkonium chloride and (b) (4) EDTA sodium as (b) (4). Each actuation of Spiriva Respimat indicated for asthma under the current NDA (#207-070) delivers 1.25-µg tiotropium. Each actuation of the currently marketed Spiriva Respimat (NDA 21-936) delivers 2.5-mcg-tiotropium.

2.4 Comments on Novel Excipients

This is not applicable. The formulation is the same as an approved and currently marketed product, Spiriva Respimat.

2.5 Comments on Impurities/Degradants of Concern

This is not applicable. This is an approved and currently marketed product.

2.6 Proposed Clinical Population and Dosing Regimen

Spiriva Respimat will be indicated for asthma in patients 12 years of age and older. A patient will use Spiriva Respimat (2 puffs) once daily (2.5 µg/day).

2.7 Regulatory Background

Spiriva Respimat is an approved and currently marketed drug product. The Agency approved the product (NDA 21-936) for a COPD indication on September 24, 2014. The current application seeks to expand the indication of the product to include asthma. A pre-NDA meeting for the application was held on December 9, 2013. No nonclinical issues were identified in the meeting.

Nonclinical characterization of tiotropium and its impurities and degradants were completed in the Spiriva applications (NDAs 21-395 and 21-936). Spiriva HandiHaler was the other marketed tiotropium product indicated for COPD. The Agency approved Spiriva HandiHaler (a dry powder inhaler) on January 30, 2004.

(b) (4)
The lower dose was a new dosage form. During the review of the application, the review team concluded that the lower dose was efficacious in asthma (b) (4). The applicant has submitted information to support approval of the lower dose (2.5-mcg/day). As such, this review will discuss the 2.5-mcg/day dose only.

The Agency approved STIOLTO Respimat (NDA 206-756) on May 21, 2015 (DARRTS ID#3762118). STIOLTO Respimat is a metered-dose inhaler of tiotropium and olodaterol in combination. The nonclinical sections of the STIOLTO Respimat labeling prompted changes in the nonclinical sections of Spiriva Respimat. See Section 12 Labeling Review for additional information.

3 Studies Submitted

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

Study #667862: 13-week inhalation toxicity study of tiotropium in juvenile rats, Report U07-2438, eCTD Section 4.2.3.7.7

Study #667862 was not reviewed because it was previously evaluated in a nonclinical review completed by Dr. Luqi Pei in IND 65,127 on August 27, 2012 (DARRTS ID# 3180610).

Study #668143: Preliminary feasibility study of tiotropium inhalation in juvenile rats, Report U08-1024, eCTD Section 4.2.3.7.7

Study #668143 was not reviewed because it was non-pivotal to the safety evaluation of the product of interest.

3.3 Previous Reviews Referenced

This review makes references to the following nonclinical reviews completed by Dr. Luqi Pei:

Original review in NDA 21-395 completed on September 20, 2002;

Original review in NDA 21-936 completed on July 29, 2008;

Labeling review in NDA 21-395 completed on July 15, 2009;

Labeling review in NDA 21-936 completed on August 24, 2014 (DARRTS ID#3616811);

Filing review of the current NDA completed on October 10, 2014 (DARRTS ID#3642422); and

IND amendment review in IND 65,127 completed on August 27, 2012 (DARRTS ID#3180610);

The review also makes references to the following nonclinical reviews completed by Dr. Andrew Goodwin in NDA 206-756:

Labeling review completed on January 23, 2015 (DARRTS ID# 3691650); and

Labeling review completed on May 18, 2015 (DARRTS ID#3758758).

4 Pharmacology

No new data was submitted. Studies characterizing the pharmacological profile of tiotropium were previously submitted to and reviewed in NDA 21-395. See nonclinical review completed by Dr. Luqi Pei on September 20, 2002, in NDA 21-395. Briefly, tiotropium is a long-acting muscarinic cholinergic receptor antagonist. It binds reversibly to muscarinic cholinergic receptors located in the airways, blocks the bronchoconstriction of acetylcholine, and results in bronchodilation.

5 Pharmacokinetics

No data was submitted. Studies characterizing the pharmacokinetic profile of tiotropium were previously submitted to and reviewed in NDA 21-395. See nonclinical review completed by Dr. Luqi Pei on September 20, 2002, in NDA 21-395. Briefly, inhaled tiotropium is readily bioavailable in animals. Tiotropium has a large volume of distribution and a long terminal half-life. Metabolism of tiotropium occurs in the liver, but non-enzymatic hydrolysis occurs in the plasma. Glucuronide conjugates were the primary metabolites in the liver. The drug is primarily excreted in the urine in unchanged form. Drug accumulation occurs in rats and a steady state is reached within three months.

6 General Toxicology

No significant new data was submitted. Studies characterizing the pharmacokinetic profile of tiotropium were previously submitted to and reviewed in NDA 21-395. See nonclinical review completed by Dr. Luqi Pei on September 20, 2002, in NDA 21-395. Tiotropium is a long-acting muscarinic cholinergic receptor antagonist. It binds reversibly to muscarinic cholinergic receptors.

7 Genetic Toxicology

Studies characterizing the carcinogenicity profile of tiotropium were previously submitted to and reviewed in NDA 21-395. Results of the studies are described in Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility of the labeling for tiotropium products (Spiriva HandiHaler and Respimat).

8 Carcinogenicity

Studies characterizing the carcinogenicity profile of tiotropium were previously submitted to and reviewed in NDA 21-395. Results of the studies are described in Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility of the labeling for tiotropium products.

9 Reproductive and Developmental Toxicology

Studies characterizing the carcinogenicity profile of tiotropium were previously submitted to and reviewed in NDA 21-395. Results of the studies are described in Section 8.1 Pregnancy and Section 13.1 of the labeling for the currently tiotropium products.

10 Special Toxicology Studies

Not applicable. No studies were submitted.

11 Integrated Summary and Safety Evaluation

Nonclinical safety of Spiriva Respimat had been established previously in two reference NDAs: Spiriva Respimat and Spiriva HandiHaler (NDAs 21-936 and 21-395, respectively). Spiriva Respimat (NDA 21-936, approved on September 24, 2014) is a product currently marketed for treatment of COPD in adults (5.0- μ g tiotropium/day). The applicant now proposed to expand the Spiriva Respimat indication to include asthma in patients 12 years of age and older (b) (4) tiotropium/day). The current submission contained no new, pivotal nonclinical studies for the safety evaluation of the current application. Nonclinical characterization of the product has been complicated in NDAs 21-936 and 21-395 (Spiriva HandiHaler). A full nonclinical review is unnecessary.

12 Labeling Review

This review recommends minor edits to the proposed text for nonclinical sections of the product. Edits were made to reflect the Division policy on labeling language. The nonclinical sections were Sections 8.1 Pregnancy and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. Content, format, and text of these sections of the proposed labeling were similar to tiotropium sections of STIOLTO Respimat labeling (NDA 206-756) that the Agency approved on May 21, 2015 (DARRTS ID#3762118). It is unnecessary to generate another detailed labeling review.

However, discussions are needed because there are significant differences in nonclinical sections between the proposed and approved labeling of Spiriva Respimat. These differences were primarily tiotropium dose ratios between animals and humans. Specifically, the proposed dose ratios were 20% greater than the ones in the approved labeling. The increases in dose ratios were not due to any differences in the recommended clinical doses between the current and previous Respimat applications (i.e., NDA 207-070 and 21-936), (b) (4)

The increases in dose ratios were rather results of a recent change in the Division's policy for nonclinical labeling review: using 60-kg patient body weight instead of the 50-kg weight used previously. This policy change had been implemented recently in the labeling review of Stiolto Respimat (DNA #206-756), a combination product of tiotropium and olodaterol. Dr. Andrew Goodwin discussed rationale and effects of the policy change on tiotropium dose ratios in the Stiolto NDA application. See Dr. Goodwin's labeling reviews completed on January 23, and May 18, 2015 (DARRTS ID# 3691650 and 3758758, respectively).

Both Stiolto Respimat and Spiriva Respimat (NDA 21-936) are indicated for COPD. (b) (4)

The nonclinical data in support of all 4 tiotropium applications (NDA 21-395, 21-936, 206-756, and 207-070) were submitted to and reviewed by the Agency under the Spiriva HandiHaler application (NDA 21-395). Because of the similarities in the recommended tiotropium clinical dose, formulation, and device characteristics between the Stiolto Respimat and Spiriva Respimat applications, the Division's recommendations on the tiotropium labeling of Stiolto Respimat are applicable to the current application.

Based on the above discussions, the review recommends changing tiotropium dose units in animals to mcg/kg/day and mcg/m² ((b) (4) respectively). These changes will keep Stiolto and Spiriva labeling consistent. The labeling of Stiolto Respimat and Spiriva Respimat uses mcg/kg/day and mg/kg/day as the tiotropium dose unit, respectively. Changing the units in Spiriva Labeling will keep the labeling of Spiriva Respimat and Stiolto Respimat in harmony.

The review finds it necessary to revise the term “recommended human daily inhalation dose (RHDID)” to “maximum recommended human daily inhalation dose (MRHDID)”. The introduction of a new, lower clinical dose by the current application prompted the edits. Lowering the clinical tiotropium dose does not affect the dose ratios between animals and humans in product labeling because the ratios in the reference products reflect the worse-case scenario, but adding the word maximum indicates that dose ratio applies to all tiotropium Respimat products.

The review noted that the dose ratio in the paragraph describing the fertility effect of tiotropium in rats (Section 13.1) in the approved Stiolto labeling has not been updated. The applicant did update dose ratios in the Spiriva labeling proposal. The updated dose ratios are acceptable.

Below are the recommended line edits (highlights) of the draft labeling proposed by the sponsor on May 15, 2015 (Sequence #0017). Underline indicates addition. Strikethroughs indicated deletion. A clean version can be found in Section 1.3.3.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m² basis at maternal inhalation doses of 1.471 and (b) (4) 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 40 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of (b) (4) 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 430 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of (b) (4) 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m² basis at inhalation doses of (b) (4) 9 and (b) (4) 88 mcg/kg/day in rats and rabbits, respectively).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to (b) (4) 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to (b) (4) 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to

(b) (4) 2 mcg/kg/day. These doses correspond to approximately 30, 40, and 0.5 times the recommended human daily inhalation dose (MRHDID) on a mcg/m² basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of (b) (4) 78 mcg/kg/day or greater (approximately 40 times the MRHDID on a mcg/m² basis). No such effects were observed at (b) (4) 9 mcg/kg/day (approximately 5 times the MRHDID on a mcg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1,689 mcg/kg/day (approximately 910 times the MRHDID on a mcg/m² basis).

13 Appendices

None

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/s/

LUQI PEI
05/22/2015

MARCIE L WOOD
05/22/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207-070

Applicant: BI

Stamp Date: August 15, 2014

Drug Name: Spiriva Respimat

NDA/BLA Type: Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. Spiriva Respimat is an approved and currently marketed product (NDA 21-936). The Agency approved the product for a COPD indication on September 24, 2014. This NDA applies for an asthma indication in patients 12 years of age and older. This NDA submission contained no pivotal nonclinical safety data. ¹
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Section 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Section 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		A pre-NDA meeting in IND (b) (4) was held on December 9, 2013. The meeting minutes (Reference ID# 3433171) states that the application may: 1) refer to NDAs 21-395 and 21-936, and 2) contain summaries and reports of the two recently completed studies of tiotropium in juvenile rats only. See comments in Section 1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. This is an approved and currently marketed product.

¹ The submission contains two nonclinical study reports which evaluate the effect of inhaled tiotropium in juvenile rats. The reports are a 13-week inhalation toxicity study of tiotropium in juvenile rats and a preliminary feasibility study of tiotropium inhalation in the juvenile rats (Studies 667862 and 668143, respectively). These studies are not considered pivotal to the safety evaluation and approvability of the proposed indication for tiotropium: asthma in patients 12 years and older.

Pharmacology/Toxicology Filing Checklist for NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable. This is an approved and currently marketed product.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. This is an approved and currently marketed product.
8	Has the applicant submitted all special studies or data requested by the Division during pre-submission discussions?	x		This is an approved and currently marketed product. Also See Comments in Sections 1 and 4.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	x		Not applicable. This is an approved and currently marketed product. No additional labeling review appears necessary.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Not applicable. This is an approved and currently marketed product.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES.

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

None

Luqi Pei, Ph.D.

October 10, 2014

Reviewing Pharmacologist

Date

Marcie Wood, Ph.D.

October 10, 2014

Supervisory Pharmacologist

Date

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

/s/

LUQI PEI
10/10/2014

MARCIE L WOOD
10/10/2014