

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-641

CHEMISTRY REVIEW(S)



NDA 21-641

AZILECT® (rasagiline mesylate) Tablets

TEVA Neuroscience

**Martha R. Heimann, Ph.D.
Division of Neurology Products**

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Chemistry Review Data Sheet

1. **NDA 21-641**
2. **REVIEW #:** 3
3. **REVIEW DATE:** 08-MAY-2006
4. **REVIEWER:** Martha R. Heimann, Ph.D.
5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	05-Sep-2003
CMC Review # 1 [W. Timmer, Ph.D.]	13-May-2004
Approvable Letter	02-Jul-2004
NDA Resubmission	04-Nov-2004
CMC Review # 2 [W. Timmer, Ph.D.]	27-Jul-2005
Approvable Letter	04-Aug-2004

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BZ)	20-Jan-2006
Amendment (AZ)	17-Mar-2006

7. **NAME and ADDRESS OF APPLICANT:**

Name: TEVA Neuroscience
Address: 425 Privet Road
Horsham, PA 19044
Representative: Dennis Williams, R.Ph.
Telephone: 215-591-8531

8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Azilect™ (Proposed)
- b) Non-Proprietary Name (USAN): rasagiline mesylate
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: S

CHEMISTRY REVIEW

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGICAL CATEGORY:

Rasagiline is a monoamine oxidase Type B (MAO-B) inhibitor indicated for treatment of idiopathic Parkinson's disease.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.5 mg, 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

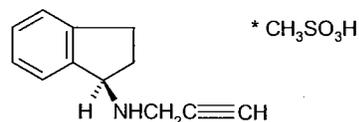
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 1H-inden-1-amine-2,3-dihydro-N-2-propynyl-(1R)-methanesulfonate

CAS No.: 161735-79-1

Molecular formula: $C_{12}H_{13}N \cdot CH_3SO_3H$

Molecular weight: 267.34



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
/	III	/	/	3	Adequate	10/09/03
/	III	/	/	4	N/A	—

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CHEMISTRY REVIEW

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45,958	Rasagiline for treatment of Parkinson's disease

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	--	--
EES	Acceptable	03-May-2005	S. Adams
LNC	N/A	--	--
Methods Validation	Regulatory methods do not require validation by FDA laboratories.	05-May-2006	M. Heimann
DMETS	Review of proposed trade name Azilect® is pending		
EA	Categorical Exclusion	01-Apr-2004	R. Timmer
Microbiology	N/A	--	--

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On Original



The Chemistry Review for NDA 21-241

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Products and Drug Substances

1. Drug Substance

The drug substance (DS), rasagiline mesylate, is a new chemical entity (NCE). It has a single chiral center and is manufactured and controlled as the (R) enantiomer. No racemization of the chiral center occurs during synthesis, long-term storage, or accelerated (stability) conditions.

A comprehensive investigation was initiated to determine the potential existence of

Rasagiline mesylate is a white to off-white crystalline powder that is freely soluble in water and ethanol.

— and have zero effect on the photostability of the drug substance.

Rasagiline mesylate is synthesized

The Manufacturing Process Development report included in the original submission of this NDA describes the changes made to the manufacturing process of pre-clinical, clinical, and production batches of rasagiline mesylate. These changes consisted primarily of

Executive Summary Section

An analysis is presented which involves potential impurities arising from the synthesis, manufacture and degradation of rasagiline mesylate. In reality, however, very few impurities are present in the drug substance.

Specifications were developed to evaluate all-important properties of rasagiline mesylate in order to assure its suitability for its intended use upon release and throughout shelf life. These specifications consist of critical quality control standards intended to confirm that all batches of DS maintain the same batch-to-batch consistency, whether used for pre-clinical, clinical, or stability batches.

Stability data that demonstrates the drug substances meets all regulatory specifications are provided for up to — for the primary stability batches, and up to — for the supporting stability batches.

2. Drug Product

The drug products are conventional immediate-release tablets containing rasagiline, 0.5 mg and 1 mg, as the mesylate salt. The tablets contain conventional pharmaceutical excipients commonly used to manufacture solid oral dosage forms. All excipients used in the manufacture of rasagiline mesylate 0.5 mg tablets comply with compendial (USP or NF) requirements.

Rasagiline mesylate is a freely soluble DS thus dissolution rate is not strongly influenced — No special dissolution studies were performed since the low dose and the dose uniformity requirements indicated — Dissolution studies performed during the development process demonstrate the rapidly dissolving nature of the product; i.e., more than — of the labeled amount of the drug substance is dissolved within 15 minutes.

Significant information is presented summarizing the development of the manufacturing process of rasagiline mesylate. In particular, the selection and optimization of the manufacturing process, as well as a comparison of the equipment and process parameters used for the manufacturing of the clinical, the primary stability batches, and the to-be-marketed formulation, is presented.

The manufacturing process consists of —

tablets and packaging. Actual data obtained during the manufacturing process and at the in-process control points indicate that, the primary stability batches, which are representative of the batches intended for marketing, comply with all acceptance criteria.

Batch analysis results for — batches of 0.5 mg tablets and — batches of 1 mg tablets demonstrate excellent batch-to-batch consistency. All rasagiline tablet batches complied with the specifications applicable at the time of release.

Rasagiline tablets are packaged into — bottles with a threaded neck. Each bottle contains 30 tablets. Two different closures are used: both are white,

Executive Summary Section

round, _____), tamper-evident screw caps _____
one cap is child-resistant (CR) while the other cap is not (non-CR). _____

_____ Appropriate information was submitted that summarized the studies that were performed in order to select a container closure system for the rasagiline mesylate tablets.

All of the primary stability studies were conducted on drug product manufactured and packaged by the intended commercial process. All stability studies demonstrate that rasagiline tablets are extremely stable; no significant changes were observed in any test parameter. Accordingly, a shelf life of 36 months for the drug product is warranted.

B. Description of How the Drug Product is Intended to be Used

Azilect® (rasagiline) is indicated as adjunctive therapy and monotherapy for treatment of Parkinson's disease (PD). The neurochemical basis of PD involves the loss of dopamine due to oxidation by monoamine oxidase B (MAO-B) that exists in the corpus striatum of the brain. Rasagiline is a selective and potent irreversible inhibitor of monoamine oxidase B (MAO-B). Thus, treatment with rasagiline results in inhibition of MAO-B activity, i.e., decomposition of dopamine, which results in increasing the level of dopamine in the brain. The recommended doses of rasagiline are 0.5 mg-1 mg/day for adjunctive therapy in PD, and 1 mg/day for monotherapy. Doses higher than 1 mg should not be used.

C. Basis for Approvability or Non-Approval Recommendation

From a CMC perspective, the sponsor has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for rasagiline mesylate and Azilect® (rasagiline) Tablets are adequately demonstrated. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the drug substance and the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. All manufacturing facilities involved in manufacture of the drug substance and finished tablets have received acceptable compliance recommendations.

III. Administrative**A. Reviewer's Signature**

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

6 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



NDA 21-641

**AGILECT®
(rasagiline mesylate)
tablets, 0.5 mg.**

-- Amendment AZ --

TEVA Neuroscience

**William C. Timmer, Ph.D.
Division of Neuropharmacologic Drug Products
HFD-120**

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Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-641
2. REVIEW #2
3. REVIEW DATE: 10 March 2005
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
IND 45,958	10 August 1994
NDA 21-641 / N(000)	05 September 2003

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
NDA 21-641 / BZ	02 March 2005
NDA 21-641 / BM	28 January 2005
NDA 21-641 / AZ	04 November 2004

7. NAME & ADDRESS OF APPLICANT:

NAME: TEVA Neuroscience
ADDRESS: 425 Privet Road, Horsham, PA 19044
REPRESENTATIVE: Denise Williams, R.Ph.
TELEPHONE: 215-591-8531

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	Agilect
NON-PROPRIETARY NAME (USAN)	Rasagiline Mesylate
CODE NAME/# (ONDC ONLY)	N/A
CHEMISTRY TYPE/SUBMISSION PRIORITY	1 S

9. LEGAL BASIS FOR SUBMISSION: 21 U.S.C. § 355

10. PHARMACOL. CATEGORY: Monoamine Oxidase Type B Inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.5 mg and 1.0 mg¹

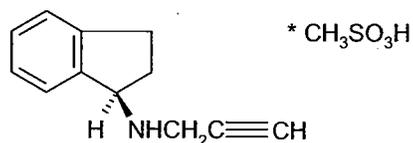
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula:	C ₁₂ H ₁₃ N • CH ₃ SO ₃ H
Molecular Weight:	267.34 g/mol
CAS No.:	161735-79-1
CAS Name:	1H-inden-1-amine-2,3-dihydro-N-2-propynyl-(1R)-methanesulfonate
INN:	Rasagiline
USAN:	Rasagiline mesylate

¹ The 1 mg tablet has been previously reviewed, and the review is available in DFS.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
/	III	/	/	1	Adequate	10/09/03
/	III	/	/	4	N/A	—

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	48,958	Rasagiline Mesylate



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-SEP-2003	S. Adams
EA	Categorical Exclusion	01-APR-2004	W.C. Timmer, Ph.D.
Methods Validation	<i>-- to be initiated --</i>	-----	W.C. Timmer, Ph.D.
ODS DMETS	Acceptable	15-JAN-2004	L.M. Wisniewski, R.N.

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On Original

The Chemistry Review for NDA 21-641

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Agilect (rasagiline mesylate) Tablets, 0.5 mg is recommended for **APPROVAL**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is rasagiline mesylate.

Rasagiline mesylate is a new chemical entity (NCE).

The drug substance (DS) rasagiline mesylate is a salt derived from methanesulfonic acid. It has a chiral center at carbon #1 and is manufactured and controlled as the (R) enantiomer. No racemization of the chiral center occurs during synthesis, long-term storage, or accelerated (stability) conditions.

A comprehensive investigation was initiated to determine the potential existence of

—
/
/

Rasagiline mesylate is a white to off-white crystalline powder that is freely soluble in water and ethanol.

— and have zero effect on the photostability of the drug substance.

Chemistry Assessment Section

Rasagiline mesylate is synthesized _____

The Manufacturing Process Development report included in the submission describes the changes made to the manufacturing process of pre-clinical, clinical, and production batches of rasagiline mesylate. These changes consisted primarily of _____

_____ ; this eliminates any concerns about cross-contamination with viral adventitious agents or TSE agents.

An analysis is presented which involves potential impurities arising from the synthesis, manufacture and degradation of rasagiline mesylate. In reality, however, very few impurities are present in the drug substance.

Specifications were developed to evaluate all-important properties of rasagiline mesylate in order to assure its suitability for its intended use upon release and throughout shelf life. These specifications consist of critical quality control standards intended to confirm that all batches of DS maintain the same batch-to-batch consistency, whether used for pre-clinical, clinical, or stability batches.

Finally, a lengthy discussion, complete with tables, is included of the stability data for each analytical test parameter. A comprehensive review of the stability data shows that the drug substances meets all regulatory specifications a) up to _____ for the primary stability batches, and 2) up to _____ for the supporting stability batches.

2. Drug Product

The drug product is rasagiline mesylate 0.5 mg tablets (expressed as rasagiline base) are provided as white to off-white, round, flat, beveled tablets. On one side of the tablets are debossed "GIL 0.5" while the other side is plain. Rasagiline mesylate tablets are packaged into _____ bottles with a threaded neck. Each bottle contains 30 tablets. Two different closures are used: both are white, round, _____ tamper-evident screw caps, one cap is child-resistant (CR) while the other cap is not (non-CR).

The batch formula for the 0.5 mg tablets was included in the submission. The batch size is _____ tablets, which is the batch size used for the manufacture of



Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

Agilect (rasagiline mesylate) is indicated for Parkinson's disease.

Parkinson's disease (PD) belongs to a group of conditions called movement disorders. PD is characterized by a combination of tremor (hands, arms, legs, jaw, face), rigidity (stiffness of the limbs and trunk), bradykinesia (slowness of movement), and postural instability (impaired balance and coordination). The symptoms vary from patient to patient and not all individuals are affected by every symptom. Indeed, in some people the disease progresses quickly, while in others it does not.

About 50,000 people are diagnosed with PD each year in the US. A million or more Americans may have this disease. PD affects both men and women almost equally. People of every race, economic class, and ethnicity can develop PD. However, age is a risk factor in that most people who develop PD are over the age of 50. The average start of the disease is age 60; however, PD has been found in a growing number of people under the age of 40. This early onset PD is not common; about 5% to 10% of the total yearly number of PD cases are early-onset. The television actor Michael J. Fox has early onset PD.

The pathophysiological basis of PD is unknown, although exposure to an unrecognized neurotoxin or the occurrence of oxidation reactions associated with the generation of free radical has been proposed. Studies aimed at finding a genetic basis to PD have not yet yielded sufficient evidence to prove that the disease is inherited. However, a recent study has found genetic evidence common to both Alzheimer's and Parkinson's disease².

The neurochemical basis of PD involves loss the loss of dopamine. Post-mortem studies revealed that the dopamine content of the substantia nigra (SN) in the brain was extremely low (less than 10% of normal). Thus the clinical symptoms are due to the degeneration of the dopaminergic neurons in the SN, resulting in a dramatic decline in dopamine level.

An obvious therapy would be to attempt to pharmacologically maintain endogenous dopamine levels. In particular, monoamine oxidase (MAO) inhibitors, which deactivate specific amine neurotransmitters through oxidation. MAO-B inhibitor selectively inhibits MAO-B that exists in corpus striatum in the brain and continuously inhibits the decomposition of dopamine, which results in increasing the level of dopamine in PD. Rasagiline is a selective and potent irreversible MAO-B inhibitor.

² Abstract P01.009: *Evidence for a Gene on Chromosome 10 that Influences Both PD and AD Susceptibility*. N. Pankratz, *et al.* 56th Annual Meeting, American Academy of Neurology, San Francisco, April 2004.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, TEVA Pharmaceuticals has submitted sufficient and appropriate information to support the approval of the drug product.

The physical and chemical characteristics, impurity profile, and stability for rasagiline mesylate 0.5 mg tablets have been adequately demonstrated in this submission.

The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the HPLC assay provides an acceptable degree of separation of rasagiline mesylate from its impurities and degradants.

Based on analysis of the stability data, the approved shelf life for Agilect (rasagiline mesylate) Tablets, 0.5 mg is 36 months at room temperature when protected from light.

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III. Administrative

A. Reviewer's Signature

/s/ William C. Timmer, Ph.D.
Review Chemist, HFD-110/810

/s/ John E. Simmons, Ph.D.
Director, HFD-810
Division of New Drug Chemistry I
Office of New Drug Chemistry

B. Endorsement Block

HFD-110/WCTimmer
HFD-810/JESimmons
HFD-120/TWheelous

C. CC Block

Original NDA 21-641

HFD-120/Division File
HFD-120/RKatz

HFD-810/JSimmons
HFD-810/HPatel

31 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling



NDA 21-641

AGILECT® (rasagiline mesylate) tablets, 1 mg.

TEVA Neuroscience

**William C. Timmer, Ph.D.
Division of Neuropharmacologic Drug Products
HFD-120**

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Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-641
2. REVIEW #1
3. REVIEW DATE: 12 May 2004
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 45,958	10 August 1994

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 21-641	5 September 2003

7. NAME & ADDRESS OF APPLICANT:

Name: TEVA Neuroscience
Address: 1090 Horsham Road
North Wales, PA 19454
Representative: J. Michael Nichols, Ph.D.
Telephone: 215-591-8531

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Agilect
Non-Proprietary Name (USAN)	Rasagiline Mesylate
Code Name/# (ONDC only)	N/A
Chemistry Type/Submission Priority	1 P

9. LEGAL BASIS FOR SUBMISSION: 21 U.S.C. § 355

10. PHARMACOL. CATEGORY: Monoamine Oxidase Type B Inhibitor

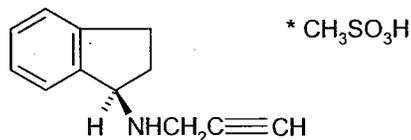
11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Formula: C₁₂H₁₃N • CH₃SO₃H

Molecular Weight: 267.34 g/mol

CAS No.: 161735-79-1

CAS Name: 1H-inden-1-amine-2,3-dihydro-N-2-propynyl-(1R)-methanesulfonate

INN: Rasagiline

USAN: Rasagiline mesylate



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
/	III	/	/	1	Adequate	10/09/03
/	III	/	/	4	N/A	—

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
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- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	48, 958	Rasagiline Mesylate



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	29-SEP-2003	S. Adams
EA	Categorical Exclusion	01-APR-2004	W.C. Timmer, Ph.D.
Methods Validation	<i>-- to be initiated --</i>	----	W.C. Timmer, Ph.D.
ODS DMETS	Acceptable	15-JAN-2004	L.M. Wisniewski, R.N.

Appears This Way
On Original

The Chemistry Review for NDA 21-641

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Agilect (rasagiline mesylate) Tablets, 1 mg is recommended for **APPROVAL**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is rasagiline mesylate.

Rasagiline mesylate is a new chemical entity (NCE).

The drug substance (DS) rasagiline mesylate is a salt derived from methanesulfonic acid. It has a chiral center at carbon #1 and is manufactured and controlled as the (R) enantiomer. No racemization of the chiral center occurs during synthesis, long-term storage, or accelerated (stability) conditions.

A comprehensive investigation was initiated to determine the potential existence of ϵ

Rasagiline mesylate is a white to off-white crystalline powder that is freely soluble in water and ethanol.

and have zero effect on the photostability of the drug substance.

Chemistry Assessment Section

Rasagiline mesylate is synthesized

The Manufacturing Process Development report included in the submission describes the changes made to the manufacturing process of pre-clinical, clinical, and production batches of rasagiline mesylate. These changes consisted primarily of

raises any concerns for cross contamination with viral adventitious agents or TSE agents.

An analysis is presented which involves potential impurities arising from the synthesis, manufacture and degradation of rasagiline mesylate. In reality, however, very few impurities are present in the drug substance.

Specifications were developed to evaluate all-important properties of rasagiline mesylate in order to assure its suitability for its intended use upon release and throughout shelf life. These specifications consist of critical quality control standards intended to confirm that all batches of DS maintain the same batch-to-batch consistency, whether used for pre-clinical, clinical, or stability batches.

Finally, a lengthy discussion, complete with tables, of the stability data for each analytical test parameter. A comprehensive review of the stability data shows that the drug substances meets all regulatory specifications a) up to for the primary stability batches, and 2) up to for the supporting stability batches.

2. Drug Product

The drug product is rasagiline mesylate 1 mg tablets (expressed as rasagiline base) are provided as white to off-white, round, flat, beveled tablets. On one side of the tablets are debossed "GIL" while the other side is plain. Rasagiline mesylate tablets are packaged into bottles with a threaded neck. Each bottle will contain 30 tablets. Two different closures are proposed: both are white, round, tamper-evident screw caps one cap is child-resistant (CR) while the other cap is not (non-CR).

The batch formula for the 1 mg tablets was included. The intended batch size is tablets, which is the batch size used for the manufacture of the three primary stability batches. The manufacturing process consists of the preparation

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_____ tablets and packaging. Actual data obtained during the manufacturing process and at the in-process control points indicate that, the primary stability batches, which are representative of the batches intended for marketing, comply with all acceptance criteria.

Rasagiline mesylate is a freely soluble DS thus dissolution rate is not strongly influenced by _____. No special dissolution was performed since the low dose and the dose uniformity requirements indicated the need _____. Dissolution studies performed during the development process demonstrate the rapidly dissolving nature of the product; *i.e.*, more than _____ of the labeled amount of the drug substance is dissolved within 15 minutes.

Significant information is presented summarizing the development of the manufacturing process of rasagiline mesylate. In particular, the selection and optimization of the manufacturing process, as well as a comparison of the equipment and process parameters used for the manufacturing of the clinical, the primary stability batches, and the to-be-marketed formulation, is presented.

All excipients used in the manufacture of rasagiline mesylate 1 mg tablets are either USP or NF.

All rasagiline mesylate tablet batches used for clinical efficacy and safety, bioavailability, bioequivalence, primary stability and other stability studies. The batch analysis results demonstrate that all batches, collected between the years 1990 through 2003, for a total of _____ batches of rasagiline mesylate drug product, excellent batch-to-batch consistency. All rasagiline mesylate drug product batches complied with the specifications applicable at the time of release.

Appropriate information was submitted that summarized the studies that were performed in order to select a container closure system for the rasagiline mesylate tablets.

All of the primary stability studies were conducted on drug product manufactured and packaged by the intended commercial process. All stability studies demonstrate that rasagiline mesylate 1 mg table are extremely stable; no significant changes were observed in any test parameter. Accordingly, a shelf life of 36 months for the drug product packaged into _____ bottles is warranted.

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B. Description of How the Drug Product is Intended to be Used

Agilect (rasagiline mesylate) is indicated for Parkinson's disease.

Parkinson's disease (PD) belongs to a group of conditions called movement disorders. PD is characterized by a combination of tremor (hands, arms, legs, jaw, face), rigidity (stiffness of the limbs and trunk), bradykinesia (slowness of movement), and postural instability (impaired balance and coordination). The symptoms vary from patient to patient and not all individuals are affected by every symptom. Indeed, in some people the disease progresses quickly, while in others it does not.

About 50,000 people are diagnosed with PD each year in the US. A million or more Americans may have this disease. PD affects both men and women almost equally. People of every race, economic class, and ethnicity can develop PD. However, age is a risk factor in that most people who develop PD are over the age of 50. The average start of the disease is age 60; however, PD has been found in a growing number of people under the age of 40. This early onset PD is not common; about 5% to 10% of the total yearly number of PD cases are early-onset. The television actor Michael J. Fox has early onset PD.

The pathophysiological basis of PD is unknown, although exposure to an unrecognized neurotoxin or the occurrence of oxidation reactions associated with the generation of free radical has been proposed. Studies aimed at finding a genetic basis to PD have not yet yielded sufficient evidence to prove that the disease is inherited. However, a recent study has found genetic evidence common to both Alzheimer's and Parkinson's disease¹.

The neurochemical basis of PD involves loss the loss of dopamine. Post-mortem studies revealed that the dopamine content of the substantia nigra (SN) in the brain was extremely low (less than 10% of normal). Thus the clinical symptoms are due to the degeneration of the dopaminergic neurons in the SN, resulting in a dramatic decline in dopamine level.

An obvious therapy would be to attempt to pharmacologically maintain endogenous dopamine levels. In particular, monoamine oxidase (MAO) inhibitors, which deactivate specific amine neurotransmitters through oxidation. MAO-B inhibitor selectively inhibits MAO-B that exists in corpus striatum in the

¹ Abstract P01.009: *Evidence for a Gene on Chromosome 10 that Influences Both PD and AD Susceptibility*. N. Pankratz, *et al.* 56th Annual Meeting, American Academy of Neurology, San Francisco, April 2004.



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brain and continuously inhibits the decomposition of dopamine, which results in increasing the level of dopamine in PD. Rasagiline is a selective and potent irreversible MAO-B inhibitor.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, TEVA Pharmaceuticals has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for rasagiline mesylate 1 mg tablets are adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the HPLC assay provides an acceptable degree of separation of rasagiline mesylate from its impurities and degradants. Based on analysis of the stability data, the approved shelf life for Agilect (rasagiline mesylate) Tablets, 1 mg is 36 months at room temperature when protected from light.

**Appears This Way
On Original**



Chemistry Assessment Section

III. Administrative

A. Reviewer's Signature

/s/ William C. Timmer, Ph.D.
Review Chemist, HFD-150

/s/ John E. Simmons, Ph.D.
Director, HFD-810
Division of New Drug Chemistry I
Office of New Drug Chemistry

B. Endorsement Block

HFD-150/WCTimmer/10-MAY-2004
HFD-810/JESimmons
HFD-120/TWheelous

C. CC Block

Original NDA 21-641

HFD-120/Division File
HFD-120/Rkatz

HFD-810/Jsimmons
HFD-810/HPatel

96 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Office of New Drug Chemistry
Division of New Drug Chemistry I

NDA FILEABILITY CHECKLIST

NDA Number: **21-641**

Drug Name: **Agilect (rasagiline mesylate) 1 mg Tablet**

Applicant: **Teva Pharmaceuticals**

Previously approved:

Stamp Date: **05-Sep-03**

Today's Date: **22-Oct-03**

IS THE CMC SECTION OF THE APPLICATION FILABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, *i.e.*, complete enough to review but may have deficiencies.

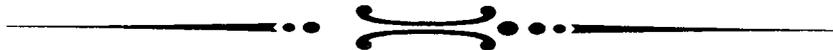
	PARAMETER	YES	NO	COMMENT
1	On its face, is the section organized adequately?	X		Electronic NDA in CTD format.
2	Is a statement provided that all facilities are ready for GMP inspection?	X		Acceptable Recommendation; 29-SEP-03
3	Has an environmental assessment report or categorical exclusion been provided?	X		Requested in Pre-NDA meeting on 30-APR-03; also included in the e-NDA.
4	Does the section contain controls for the drug substance?	X		
5	Does the section contain controls for the drug product?	X		
6	Has stability data and analysis been provided to support the requested expiration date?		X	— of data included; sponsor requests 36 mo. expiry
7	Have draft container labels been provided?	X		
8	Has the draft package insert been provided?	X		
9	Is there a Methods Validation package?	X	X	Need 2 more copies of MV package
10	Is a separate microbiological section included? Is a micro consult needed?	X		No; tablet, non-sterile.

Regarding the DMFs:

DMF NUMBER	HOLDER	DESCRIPTION	LOA INCLUDED	DATE OF LAST REVIEW
—	—	Type III	9/04/2001	October 2003
—	—	Type III	4/04/2003	In progress

Regarding the DS and DP: The DS section contains a comprehensive list of impurities (plus concentrations and methods of assay).

The DP consists of a 1 mg tablet consisting of standard compendial excipients.



Overall Comment(s): The sponsor has had significant interactions with FDA; the last being a pre-NDA meeting in April 2003. The NDA appears to be well organized with the appropriate data set. Regulatory review should not require a significant effort.

/s/ William C. Timmer, Ph.D.