CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-720

Chemistry Review(s)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720 CHEM.REVIEW # 5 REVIEW DATE: 18-OCT-04

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-DEC-03	18-DEC-04	05-JAN-04
Amendment	04-OCT-04	04-OCT-04	04-OCT-04

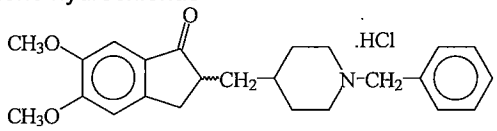
NAME & ADDRESS OF APPLICANT: Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) ODT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#:
Chem.Type/Ther.Class: AChEsterase Inhibitor/2013060

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Tablets
STRENGTHS: 5 mg & 10 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl
CAS name: (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C24H29NO3.HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0
SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)



RELATED DOCUMENTS: none

REMARKS/COMMENTS: The newly proposed full proprietary name [ ] Aricept ODT (donepezil hydrochloride orally disintegrating tablets) is unacceptable. The sponsor must change it to: Articept ODT (donepezil hydrochloride) orally disintegrating tablet. In addition, the OC withdrew the acceptable overall recommendation and is now waiting for the GMP inspection to take place in the future (Kashima/Kawashima problem).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 21-720 APPROVABLE, subject to the resolution of proprietary name issue and the completion of inspection.

cc:
Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.005.doc

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/s/

Janusz Rzeszotarski
10/18/04 09:03:46 AM
CHEMIST

Maryla Guzewska
10/18/04 09:12:17 AM
CHEMIST

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720 CHEM.REVIEW # 4 REVIEW DATE: 27-SEP-04

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-DEC-03	18-DEC-03	05-JAN-04

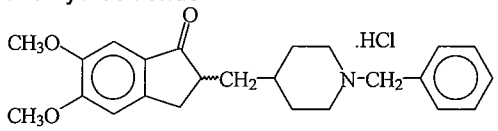
NAME & ADDRESS OF APPLICANT: Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) ODT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#:
Chem.Type/Ther.Class: AChEsterase Inhibitor/2013060

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Tablets
STRENGTHS: 5 mg & 10 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl
CAS name: (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C24H29NO3.HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0
SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)



RELATED DOCUMENTS: none

REMARKS/COMMENTS: The Office of Compliance issued an overall recommendation of all facilities now being acceptable. (see the attached copy of EER). Therefore, the only still remaining issue is the unfortunate attempt to call Aricept Orally Disintegrating Tablets by the name .

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 21-720 APPROVABLE, subject to the resolution of proprietary name issue.

cc:
Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.004.doc

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/s/

Janusz Rzeszotarski
9/27/04 12:10:44 PM
CHEMIST

Maryla Guzewska
9/28/04 08:13:00 AM
CHEMIST

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720 CHEM.REVIEW # 3 REVIEW DATE: 16-SEP-04

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-DEC-03	18-DEC-03	05-JAN-04
Amendment (BL)	03-SEP-04	07-SEP-04	08-SEP-04

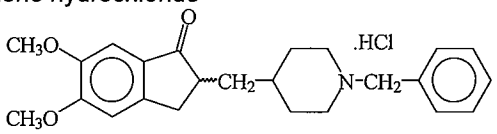
NAME & ADDRESS OF APPLICANT: Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) ODT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#:
Chem.Type/Ther.Class: AChEsterase Inhibitor/2013060

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Tablets
STRENGTHS: 5 mg & 10 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl
CAS name: (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C24H29NO3.HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0



SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)
RELATED DOCUMENTS: none
REMARKS/COMMENTS: In the response to request to change the name from Aricept ® Rapidly Disintegrating Tablets to Aricept ® Orally Disintegrating Tablets the sponsor brings in a new name: [ ] donepezil HCl) orally disintegrating tablets. This proposed, new, proprietary name has never been reviewed by the DMETS and is unacceptable. Therefore, both, the proposed drafts of commercial presentations and labeling are unacceptable. The sponsor was urged to combine the labeling for all three formulations. Instead a separate labeling for the [ ] was submitted. The proprietary name must be either reviewed by DMETS or changed back to the proposed name: Aricept ® (donepezil HCl) orally disintegrating tablets.

CONCLUSIONS & RECOMMENDATIONS: There is one facility still waiting for the EER recommendation as of 15-SEP-2004. Recommend NDA 21-720 APPROVABLE, subject to: OC EER recommendation and to resolution of the proprietary name issue.

cc:
Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.003.doc

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/s/

Janusz Rzeszotarski
9/17/04 07:32:00 AM
CHEMIST

John Simmons
9/20/04 11:05:17 AM
CHEMIST
for M Guzewska

NDA 21-720

Aricept (donepezil HCl) Orally Disintegrating Tablets

Eisai Medical Research

Chemistry Review
W. Janusz Rzeszotarski, Ph.D.
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. **NDA #** 21-720

2. **REVIEW #:** 2

3. **REVIEW DATE:** 12-JUL-2004

4. **REVIEWER:** W. Janusz Rzeszotarski, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Original	17-DEC-04

6. **SUBMISSION(S) BEING REVIEWED: An amended submission.**

Submission(s) Reviewed	Document Date
Amendment (BC)	01-MAR-04
Amendment (BC)	04-MAR-04
Amendment (BC)	17-MAY-04
Amendment (BC)	11-AUG-04

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

Name: Eisai Medical Research
Address: 500 Frank W. Burr Blvd
Jersey City, NJ 07311

Representative: Charles J. Callagan
Telephone: 201-287-2242

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary: Aricept ODT
   b) Non-Proprietary: Donepezil hydrochloride
   c) Code Name/#
   d) Chem. Type/Submission Priority: 3S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Treatment of moderate to severe Alzheimer's Disease

11. **DOSAGE FORM:** Orally disintegrating tablet

12. **STRENGTH/POTENCY:** 5 mg & 10 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __X__ **Rx** ___ **OTC**

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) **NO**

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

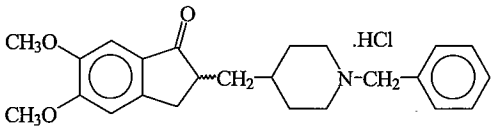
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl

CAS name: (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride

Molecular formula: C24H29NO3.HCl

Relative molecular mass: Mr = 415.95

CAS Registry number: 142057-77-0



16. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	I	[redacted]		3	Adequate	25-APR-2002	Packaging/ blister
[redacted]	III			3	Adequate	05-AUG-1999	Packaging/ blister
[redacted]	II			3	Adequate	22-MAY-2001	Packaging/ blister
[redacted]	III			3	Adequate	27-SEP-2000	Packaging/ blister

[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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Eisai – Cholinesterase Inhibitor
IND		
IND		
IND		
NDA	20-690 AP 25-NOV-1996	Eisai –Aricept Tablets – AD
NDA	21-719 PN 18-DEC-2003	Eisai – Aricept Oral Solution

18. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	In review		
EES	Submitted to OC	04-FEB-2004	PN as of 25-AUG-2004
Pharm/Tox	In review		
Biopharm	In review		Robert Kumi, Ph.D.
Methods Validation	Acceptable	30-JUN-2004	W. Janusz Rzeszotarski, Ph.D
EA	Acceptable	30-JUN-2004	W.Janusz Rzeszotarski, Ph.D.
Microbiology	In review		
DMETS	Acceptable	01-JUN-04	Linda Wisniewski, R.Ph.

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Aricept ODT (Orally Disintegrating Tablets) are tablets containing 5 or 10 mg of donepezil hydrochloride. The application refers to the approved NDA 20-690 for the information on donepezil hydrochloride drug substance. The manufacturer, the method of manufacture and the specifications for the drug substance have not been changed. The need for the orally disintegrating tablet designed for the AD patients is well justified (impaired salivation, coordination and swallowing). The tablet manufacturing technique is well established and proven for other similar drug products (Risperdal M-Tabs, Claritin RediTabs, Zubrin, etc.). The 5 mg and 10 mg investigational formulations used in the bioequivalence studies and the proposed commercial formulations are the same. Investigational formulations were produced at a batch size of [ ] tablets. The commercial batch size is [ ] tablets. ~ commercial scale batches manufactured at the proposed Eisai Co. Ltd. commercial manufacturing (ECL-Misato) facility in Misato, Japan and ~ pilot scale batches manufactured at the Eisai Co. Ltd. Formulation Research Laboratory in Kawashima, Japan met the proposed release specifications. Primary stability is provided for three lots each of the 5 mg and 10 mg donepezil hydrochloride orally disintegrating tablets in the container/closure system intended for marketing. The primary stability batches were manufactured at ECL-Misato at full scale using the commercial formulation and equipment and packaged at the Eisai Inc. (ESI-RTP) facility in Research Triangle Park, North Carolina, the proposed packaging site. Supportive stability data is provided including data on these and other batches packaged into container/closure configurations not selected for marketing.

Potential degradation products of donepezil hydrochloride in the drug products will be monitored as follows: [ ] The proposed limits are supported by available stability data on the new dosage form and are consistent with the limits for approved Aricept Tablets in NDA 20-690 and recommended ICH limits for identified and unidentified impurities in the ICH Guidelines for Impurities in New Drug Products (February 5,2003).

The sponsor provided satisfactory data to prove the reproducibility of manufacturing process and the purity and stability of the drug product.

The Establishment Evaluation System still shows two of the listed facilities scheduled for inspection as of 25-AUG-2004. The RFI of 17-JUN-04 produced response on 11-AUG-04, which addresses the total levels of impurities/degradants in the drug product. Therefore, at present the application has to be recommended as APPROVABLE subject to establishment evaluation and establishment of proper (Orally instead Rapidly) name for the drug product.

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

N/A

II. Summary of Chemistry Assessments

Donepezil hydrochloride is an inhibitor of acetylcholine esterase that shows a decreased level of side effects. The rapidly disintegrating formulation will assist the patients with impaired swallowing ability (decreased salivation, impaired coordination and swallowing).

A. Description of the Drug Product and Drug Substance

Drug Product. The proposed commercial products are orally disintegrating tablets containing 5 or 10 mg of donepezil hydrochloride. The 5 mg dosage strength is a round, white tablet with a diameter of 9.5 mm and a tablet weight of 280 mg. The 10 mg dosage strength is a round, yellow tablet with a diameter of 9.5 mm and tablet weight of 280 mg. The tablets are differentiated by embossing and color. The manufacturing process involves [ ] The tablets [ ] consisting of donepezil hydrochloride, mannitol, carrageenan, colloidal silicon dioxide, and purified water. [ ] with mannitol (and yellow ferric oxide for the 10 mg dosage form). The granules [ ] polyvinyl alcohol solution, [ ]. The 5 mg and 10 mg investigational formulations used in the bioequivalence studies and the proposed commercial formulations are the same. Investigational formulations were produced at a batch size of [ ] tablets. The commercial batch size is [ ] tablets. — commercial scale batches manufactured at the proposed Eisai Co. Ltd. commercial manufacturing (ECL-Misato) facility in Misato, Japan and — pilot scale batches manufactured at the Eisai Co. Ltd. Formulation Research Laboratory in Kawashima, Japan met the proposed release specifications. **Primary stability is provided for three lots each of the 5 mg and 10 mg donepezil hydrochloride rapid disintegration tablets in the container/closure system intended for marketing.** The primary stability batches were manufactured at ECL-Misato at full scale using the commercial formulation and equipment and packaged at the Eisai Inc. (ESI-RTP) facility in Research Triangle Park, North Carolina, the proposed packaging site. Supportive stability data is provided including data on these and other batches packaged into container/closure configurations not selected for marketing.
Potential degradation products of donepezil hydrochloride in the drug products will be monitored as follows [ ] The proposed limits are supported by available stability data on the new dosage form and are consistent with the limits for approved Aricept Tablets in NDA 20-690 and recommended ICH limits for identified and unidentified impurities in the ICH Guidelines for Impurities in New Drug Products (February 5,2003).
The ongoing primary stability studies will be monitored through — months. Additionally, the first three commercial production batches of each strength will be monitored for stability through — months in accordance with the post approval stability protocol and commitment.

Drug Substance. Donepezil hydrochloride is a very well characterized drug substance (NDA 20-690) of noticeable stability. No detectable degradation was observed in various containers like: — bags, — glass bottles or — tubes. Similarly donepezil was studied in acidic, basic and neutral conditions showing no degradation. Only in extremely harsh conditions of high temperature and oxidation a slight degradation was observed.

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

Aricept RDT is provided in two strengths of 5 mg and 10 mg marketed in peelable blisters only. A film/aluminum foil, unit dose blister of peelable type consisting of 30 tablets will be packaged in an aluminum pouch. All packaging components are suitable for pharmaceutical or food contact use.

The standard room temperature storage is recommended and the requested expiration date of 24 months is justified.

C. Basis for Approvability or Not-Approval Recommendation

A stable formulation and a proven stability of API. The API and drug product specifications justified. **The Establishment Evaluation System still shows two of the listed facilities scheduled for inspection as of 25-AUG-2004. The RFI of 17-JUN-04 produced response on 11-AUG-04, which addresses the total levels of impurities/degradants in the drug product. Therefore, at present the application has to be recommended as APPROVABLE subject to establishment evaluation and establishment of proper (Orally instead Rapidly) name for the drug product.**

III. Administrative

Chemist: W. Janusz Rzeszotarski, Ph.D./25-AUG-2004

ChemistryTeamLeader/ Date: Maryla E. Guzewska, Ph.D.

Project Manager / Date: Melina Griffis, R.Ph

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720 CHEM.REVIEW # 2 REVIEW DATE: 25-AUG-04

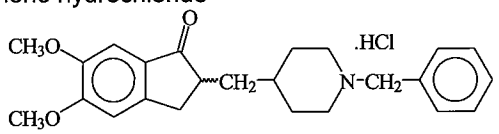
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-DEC-03	18-DEC-03	05-JAN-04
Amendment (BC)	01-MAR-04	02-MAR-04	08-MAR-04
Amendment (BC)	04-MAR-04	05-MAR-04	12-MAR-04
Amendment (BC)	17-MAY-04	18-MAY-04	23-MAY-04
Amendment (BC)	11-AUG-04	12-AUG-04	17-AUG-04

NAME & ADDRESS OF APPLICANT: Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) RDT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#:
Chem.Type/Ther.Class: AChEsterase Inhibitor/2013060

PHARMACOL.CATEGORY/INDICATION: AD
DOSAGE FORM: Rapidly Disintegrating Tablets
STRENGTHS: 5 mg & 10 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl
CAS name: (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: $C_{24}H_{29}NO_3.HCl$
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0



SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)
RELATED DOCUMENTS: none
REMARKS/COMMENTS: Aricept RDT (Rapidly Disintegrating Tablets) are tablets containing 5 or 10 mg of donepezil hydrochloride. The application refers to the approved NDA 20-690 for the information on donepezil hydrochloride drug substance. The manufacturer, the method of manufacture and the specifications for the drug substance have not been changed. The need for the rapidly disintegrating tablet designed for the AD patients is well justified (impaired salivation, coordination and swallowing). The tablet manufacturing technique is well established and proven for other similar drug products (Risperdal M-Tabs, Claritin RediTabs, Zubrin, etc.). The 5 mg and 10 mg investigational formulations used in the bioequivalence studies and the proposed commercial formulations are the same.
CONCLUSIONS & RECOMMENDATIONS: The sponsor provided satisfactory data to prove the reproducibility of manufacturing process and the purity and stability of the drug product. **The Establishment Evaluation System shows two of the listed facilities still scheduled for inspection as of 28-AUG-2004. The RFI response (see the attached E-mail) has to address the total of impurities present. Therefore, at present, the application has to be recommended as APPROVABLE subject to establishment evaluation and RFI response.**

cc: Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.002.doc

25 Page(s) Withheld

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____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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/s/

Janusz Rzeszotarski
8/26/04 09:08:50 AM
CHEMIST

Maryla Guzewska
8/26/04 09:22:53 AM
CHEMIST