CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-756

CHEMISTRY REVIEW(S)
NDA 21-756

Macugen®

(pegatanib sodium) 0.3 mg/90 µl injection

Eyetech Pharmaceuticals

Hossein S. Khorshidi
Division of Anti-Inflammatory/Analgesics & Ophthalmic Drug Products
HFD-550
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Chemistry Review Data Sheet

1. NDA # 21-756

2. REVIEW # 1

3. REVIEW DATE:  12/14/04

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:
   None

6. SUBMISSION(S) BEING REVIEWED (Drug Substance Section Only):

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7. NAME & ADDRESS OF APPLICANT:

   Name: Eyetech Pharmaceuticals

   Address: 140 east Hanover Avenue, cedar Knolls, New Jersey 07927

   Representative: Karen Fleshman, Director, Regulatory affairs

   Telephone: (973)-775-4506
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Macugen®
   b) Non-Proprietary Name (USAN): Pagatanib Sodium
   c) Code Name #: N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: Rolling NDA, P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg/90 μl injection

13. ROUTE OF ADMINISTRATION: Intravitreous Injection

14. Rx/OTC DISPENSED: ___X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ____SPOTS product – Form Completed
    ___X___ Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

IUPAC: (2-deoxy-2-fluorocytidylyl-(3′→5′) O-phosphoryl)-2′-methoxyguanosylyl-(3′→5′) O-phosphoryl)-2′-methoxyguanosylyl-(3′→5′) O-phosphoryl)-riboadenosylyl-(3′→5′) O-phosphoryl)-riboadenosylyl-(3′→5′) O-phosphoryl)-2′-deoxy-2′-fluorouridylyl-(3′→5′) O-phosphoryl)-2′-deoxy-2′-fluorouridylyl-(3′→5′) O-phosphoryl)-2′-methoxyadenosylyl-(3′→5′) O-phosphoryl)-2′-deoxy-2′-fluorouridylyl-(3′→5′) O-phosphoryl)-2′-methoxyguanosylyl-(3′→5′) O-phosphoryl)

or


or

Chemical Structure

Where R is

![Chemical Structure](image)

and n is approximately 450.
Chemistry Review Data Sheet

Molecular Weight: Oligonucleotide moiety: ~ (free acid) ~ (sodium salt)
: PEG-conjugated oligo: ~ (free acid), 50.0 Kilodalton (sodium salt)

Molecular Formula: C_{284}H_{326}N_{101}O_{183}P_{23}F_{13}Na_{28} (salt form of oligo-moiety)
C_{10}H_{17}N_{12}O_{5} (C_{2}H_{4}O)_{n} (polyethylene glycol portion, i.e. R above)

CAS # 222716-86-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (for the drug substance only):

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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:

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The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, the drug substance section of this NDA application is recommended for Approval.

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

None.

II. Summary of Chemistry Assessments

NDA 21-756 was accepted as a Continuous Marketing Application (CMA), pilot 1-reviewable units for fast track products under PDUFA. Eyetech Pharmaceuticals has requested a priority review for this application.

A. Description of the Drug Substance(s)

Pegaptanib sodium is a pegylated modified ribonucleic acid (RNA) oligonucleotide (28-mer) developed for the treatment of age-related macular degeneration (AMD). The chemically modified sugars confer stability against nuclease degradation and the covalently attached PEG moiety increases the residence time of the molecule in the vitreous. The drug substance binds specifically to vascular endothelial growth factor (VEGF), inducing the inhibition of angiogenesis. Pegaptanib sodium is 

The drug substance

Characterization and proof of structure has been accomplished using several methods, including:

The impurity profile consists of impurities. A is used for manufacturing of this drug substance. The manufacturing process consists of substance is in form of . Several in-process tests and controls are included. The critical in-process controls are identified as:

The drug substance specification include the following test attributes:
Based on CMC recommendation, the proposed acceptance criteria for the following test attributes were revised:

- Pegaptanib sodium is stored in 

The status of all referenced DMFs are adequate. The stability program and testing have been performed according to ICH guidelines. The primary stability batches were studied through, recommended storage conditions, and 5 °C (± 3 °C), accelerated storage conditions. In addition, up to of stability data on batches stored at recommended and accelerated storage conditions are also submitted. The submitted stability data support the proposed of retest period for this drug substance when stored at -20 °C (± 5 °C) and

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

Refer to the Drug Product review section by Dr. Libaniel Rodriguez, HFD-550.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission has provided adequate information on the chemistry, manufacturing and controls for the manufacturing of the drug substance, Pegaptanib Sodium. The characterization and proof of structure have been established. Adequate in-process controls are placed through the manufacturing process. The drug substance specification and proposed acceptance criteria are acceptable and adequately control the quality of the final drug substance.

III. Administrative

A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (signed electronically in DFS).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hossein Khorshidih
12/14/04 03:07:25 PM
CHEMIST

Linda Ng
12/15/04 09:55:56 AM
CHEMIST
This is the drug substance review of the NDA
NDA 21-756

Macugen (pegaptanib sodium injection) 0.3 mg/90 (market product) and 1.0 mg/90 μL (currently not intended for marketing)

Chemistry Review 2

EYETECH Pharmaceuticals

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550
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   A. Reviewer’s Signature .......................................................................................................................... 10
   B. Endorsement Block ........................................................................................................................... 10
   C. CC Block .......................................................................................................................................... 10

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Chemistry Review Data Sheet

1. NDA 21-756
2. REVIEW #: 2
3. REVIEW DATE: 17-DEC-2004
4. REVIEWER: Libaniel Rodriguez
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6. SUBMISSION(S) BEING REVIEWED: (Drug Product Sections Only)

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7. NAME & ADDRESS OF APPLICANT:
   Name: EYETECH Pharmaceuticals
   Address: 3 Times Square, 12th Floor, New York, NY 10036
   Representative: Loni da Silva
   Vice-President Global Regulatory Affairs
   Telephone: 212 824 3166

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: MACUGEN
   b) Non-Proprietary Name (USAN): pegaptanib sodium
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF Inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg — mg based on oligonucleotide weight per 90 μL

13. ROUTE OF ADMINISTRATION: Intravitreal injection. One injection every six weeks for at least one year

14. Rx/OTC DISPENSED: _X_Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    _X_Not a SPOTS product

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

   RNA, ((2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-
G_{m}(2'-deoxy-2'-fluoro)U-G_{m-1}A_{m-1}(2'-deoxy-2'-fluoro)U-G_{m-2}(2'-deoxy-2'-fluoro)C-(2'-
deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_{m-2}(2'-deoxy-2'-fluoro)U-A_{m-3}(2'-deoxy-2'-fluoro)C-A_{m-}
(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_{m}(3'\rightarrow 3')-dT_{5}, 5'-ester with 
\alpha,\alpha'-(4,12-dioxo-6-[[5-(phosphonoxy)pentyl]amino carbonyl]-3,13-dioxa-5,11-diaza-1,15-
pentadecanediyl]bis[6-methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

Chemical Structure

Where R is
\[
\begin{align*}
\text{Me} & \text{O} - \text{H} \quad \text{O} - \text{NH} - \text{NH}_2 \\
\text{Me} & \text{O} - \text{T}
\end{align*}
\]

and n is approximately 450.

The molecular formula for pegaptanib sodium is C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}\left[C_2H_2O\right]_n 
(where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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:

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The Chemistry Review for NDA 21-756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product section of this application is recommended for an Approvable Action.

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

In the amendments of November 10 and December 9, 2004, EyeTech made a commitment to provide a drug product prior to marketing. However, at this time there is no sterility data or a proposal to validate the sterilization process to verify that the

II. Summary of Chemistry Assessments

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

Macugen drug product is a sterile aqueous solution containing pegaptanib sodium for intravitreous injection. The product is supplied in single-dose pre-filled 1 mL capacity glass syringes sealed with a rubber plunger. The syringe has a fixed 27 gauge needle with a gray rubber needle shield and a rigid outer shield. The syringe is packed in a foil pouch. Another sealed foil pouch holds a polystyrene plunger and a white flange. Both pouches are packaged in a carton.

Macugen is formulated as a 3.47 mg/mL solution to deliver 0.3 mg of the oligonucleotide pegaptanib free acid. The volume for delivering is 90 μL.

The 0.3 mg/90μL will be commercially marketed when approved.

Description of the Drug Substance(s)

Pegaptanib sodium is a pegylated modified ribonucleic acid (RNA) oligonucleotide (28-mer) developed for the treatment of age-related macular degeneration (AMD). The
chemically modified sugars confer stability against nuclease degradation and the covalently attached PEG moiety increases the residence time of the molecule in the vitreous. The drug substance binds specifically to vascular endothelial growth factor (VEGF), inducing the inhibition of angiogenesis. Pegaptanib sodium is is The drug substance

Characterization and proof of structure has been accomplished using several and methods, including:

The impurity profile consists of impurities. A is used for manufacturing of this drug substance. The manufacturing process consists of and the final drug substance is in form of . Several in-process tests and controls are included. The critical in-process controls are identified as:

The drug substance specification include the following test attributes:

Based on CMC recommendation, the proposed acceptance criteria for the following test attributes were revised:

Pegaptanib sodium is stored in

The status of all referenced DMFs are adequate. The stability program and testing have been performed according to ICH guidelines. The primary stability batches were studied through at -20°C (± 5°C), recommended storage conditions, and 5°C (± 3°C), accelerated storage conditions. In addition, up to of stability data on 3 supportive batches stored at recommended and accelerated storage conditions are also submitted. The submitted stability data support the proposed of retest period for this drug substance when stored at -20°C (± 5°C) and .

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

The Macugen pre-filled syringes contain of the drug product. The intention is to deliver a minimum volume of 90 μL intravitreally in an aseptic environment. The plunger must be carefully screwed into the rubber stopper prior to injection. The 0.3 mg marketed dosage form is to be injected in patients with exudative age related macular degeneration every 6 weeks for a period of 54 weeks.

The expiration period of the 0.3 mg/90μL Macugen drug product is 15 months when stored at 2°C to 8°C.
CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

No data or validated sterilization process are available to verify the chemistry review 1B dated December 8, 2004.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistryTeamLeader: Linda Ng, Ph.D. HFD-550/830/17-DEC-2004
ProjectManager: Puglisi Mike HFD-550/17-DEC-2004

C. CC Block

NDA 21756
Wiley Chambers, MD. HFD-550/17-DEC-2004
Lin David. Ph.D. HFD-830/17-DEC-2004
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/s/
Libaniel Rodriguez
12/17/04 01:10:23 PM
CHEMIST
Review #2 drug product section, labeling

Linda Ng
12/17/04 01:51:39 PM
CHEMIST
NDA 21-756

Macugen (pegaptanib sodium injection) 0.3 µL

Chemistry Review 1B

EYETECH Pharmaceuticals

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550
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Chemistry Review Data Sheet

1. NDA 21-756

2. REVIEW #: 1B

3. REVIEW DATE: 08-DEC-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

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6. SUBMISSION(S) BEING REVIEWED: (Drug Product Sections Only)

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7. NAME & ADDRESS OF APPLICANT:
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: MACUGEN
   b) Non-Proprietary Name (USAN): pegaptanib sodium
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1
      • Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF Inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg — based on oligonucleotide weight per 90 μL

13. ROUTE OF ADMINISTRATION: Intravitreal injection. One injection every six weeks for at least one year

14. Rx/OTC DISPENSED: ___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product — Form Completed

    ___X___Not a SPOTS product

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

RNA, ((2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-
Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-
deoxy-2'-fluoro)U-(2'-deoxy-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)C-Am-
(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT, 5'-ester with α,α'-[4,12-dioxo-6-[[5-(phosphoonoxy)penty]amino]carbonyl]-3,13-dioxo-5,11-diaza-1,15-pentadecanediyl]bis[methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

**Chemical Structure**

Where R is

\[
\text{R} = \text{Me} \text{O} \bigg( \text{CH}_2 \bigg)[\text{CH} \bigg][\text{CH}_2 \bigg][\text{CH}\bigg]
\]

and n is approximately 450.

The molecular formula for pegaptanib sodium is \( C_{294}H_{447}F_{13}N_{107}Na_{28}O_{189}P_{28}(C_2H_4O)_n \) (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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:

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The Chemistry Review for NDA 21-756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product section of this application is recommended for an Approvable Action.

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

In the amendments of November 10 and December 9, 2004, EyeTech made a commitment to provide a drug product prior to marketing. However, at this time there is no or a proposal to

II. Summary of Chemistry Assessments

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

See chemistry review 1A for the drug substance section.

Macugen drug product is a sterile aqueous solution containing pegaptanib sodium for intravitreous injection. The product is supplied in single-dose pre-filled 1 mL capacity glass syringes sealed with a rubber plunger. The syringe has a fixed 27 gauge needle with a gray rubber needle shield and a rigid outer shield. The syringe is packed in a foil pouch. Another sealed foil pouch holds a polystyrene plunger and a white flange. Both pouches are packaged in a carton.

Macugen is formulated as a 3.47 mg/mL solution to deliver 0.3 mg of the oligonucleotide pegaptanib free acid. The volume for delivering is 90 μL. The 0.3 mg/90μL will be commercially marketed when approved.
B. Description of How the Drug Product is Intended to be Used

The Macugen pre-filled syringes contain 90 — μL of the drug product. The intention is to deliver a minimum volume of 90 μL intravitreally in an aseptic environment. The plunger must be carefully screwed into the rubber stopper prior to injection. The 0.3 mg marketed dosage form is to be injected in patients with exudative age related macular degeneration every 6 weeks for a period of 54 weeks.

The expiration period of the 0.3 mg/90μL Macugen drug product is 15 months when stored at 2°C to 8°C.

C. Basis for Approvability or Not-Approval Recommendation

No data or validated sterilization process are available to verify the — . Details are described in pages 41 and 42 of this review.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Chemist: Libaniel Rodriguez, Ph.D. HFD-550/830/14-DEC-2004
ChemistryTeamLeader: Linda Ng, Ph.D. HFD-550/830/14-DEC-2004
ProjectManager: Puglisi Mike HFD-550/14-DEC-2004

C. CC Block

NDA 21756
Wiley Chambers, MD. HFD-550/14-DEC-2004
Lin David. Ph.D. HFD-830/14-DEC-2004
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/s/
Libaniel Rodriguez
12/15/04 09:37:12 AM
CHEMIST
Macugen drug product NDA section review, approvable

Linda Ng
12/15/04 10:06:22 AM
CHEMIST
This is the drug product review of the NDA