

COR

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information, please refer to 21 C.F.R. § 314.53.

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA # 20-961

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- X Trade Name: VitraveneTM
- X Active Ingredient(s) Fomivirsen sodium
- X Strength(s): 6.6 mg / mL
- X Dosage Form: Injection
- X Approval Date: (to be determined)

A. This section should be completed for each individual patent

U.S. Patent Number: 4,689,320

Expiration Date: October 15, 2004

Type of Patent-Indicate all that apply:

- X Drug Substance (Active Ingredient) Y X N
- X Drug Product (Composition/Formulation) X Y N
- X Method of Use X Y N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

The method for which approval is being sought is treatment of cytomegalovirus (CMV) retinitis in a human patient by intravitreal administration of a phosphorothioate oligonucleotide which is capable of hybridizing with CMV mRNA.

Name of Patent Owner: Isis Pharmaceuticals, Inc.

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

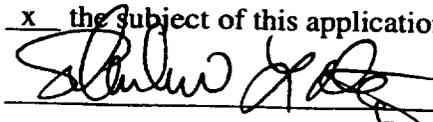
The undersigned declares that the above stated United States Patent Number 4,689,320 covers the composition, formulation and/or method of use of Fomivirsen (name of drug product). This product is:

X currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:



(Mark W. Lotz, R.Ph.)

Date:

6 April 1998

Title (optional):

Executive Director, Regulatory Affairs

Telephone Number (optional):

(760) 603-2378

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,^o a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Location address: (For FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301) 594-6463

^o - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information, please refer to 21 C.F.R. § 314.53.

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA # 20-961

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

X Trade Name: VitraveneTM
X Active Ingredient(s) Fomivirsen sodium
X Strength(s): 6.6 mg / mL
X Dosage Form: Injection
X Approval Date: (to be determined)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,264,423

Expiration Date: November 23, 2010

Type of Patent-Indicate all that apply:

X Drug Substance (Active Ingredient) x Y N
X Drug Product (Composition/Formulation) x Y N
X Method of Use x Y N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

The method for which approval is being sought is treatment of cytomegalovirus (CMV) retinitis in a human patient by intravitreal administration of a phosphorothioate oligonucleotide which is capable of hybridizing with CMV mRNA.

Name of Patent Owner: The United States of America as represented by the Department of Health and Human Services

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

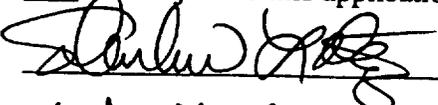
B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,264,423 covers the composition, formulation and/or method of use of Fomivirsen (name of drug product). This product is:

X currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:  (Mark W. Lotz, R.Ph.)

Date: 6 April 1998

Title (optional): Executive Director, Regulatory Affairs

Telephone Number (optional): (760) 603-2378

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,^o a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Location address: (For FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301) 594-6463

^o - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information, please refer to 21 C.F.R. § 314.53.

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA # 20-961

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:.

X Trade Name: VitraveneTM
X Active Ingredient(s) Fomivirsen sodium
X Strength(s): 6.6 mg / mL
X Dosage Form: Injection
X Approval Date: (to be determined)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,276,019

Expiration Date: January 4, 2011

Type of Patent-Indicate all that apply:

X Drug Substance (Active Ingredient) x Y N
X Drug Product (Composition/Formulation) x Y N
X Method of Use x Y N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

The method for which approval is being sought is treatment of cytomegalovirus (CMV) retinitis in a human patient by intravitreal administration of a phosphorothioate oligonucleotide which is capable of hybridizing with CMV mRNA.

Name of Patent Owner: The United States of America as represented by the Department of Health and Human Services

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

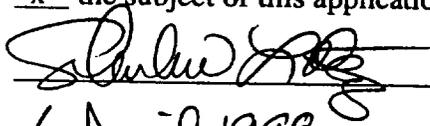
B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,276,019 covers the composition, formulation and/or method of use of Fomivirsen (name of drug product). This product is:

X currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:  (Mark W. Lotz, R.Ph.)

Date: 6 April 1998

Title (optional): Executive Director, Regulatory Affairs

Telephone Number (optional): (760) 603-2378

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,^o a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Location address: (For FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301) 594-6463

^o - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information, please refer to 21 C.F.R. § 314.53.

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA # 20-961

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

X Trade Name: VitraveneTM
X Active Ingredient(s) Fomivirsen sodium
X Strength(s): 6.6 mg / mL
X Dosage Form: Injection
X Approval Date: (to be determined)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,442,049

Expiration Date: August 15, 2012

Type of Patent-Indicate all that apply:

X Drug Substance (Active Ingredient) X Y N
X Drug Product (Composition/Formulation) Y X N
X Method of Use Y X N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Isis Pharmaceuticals, Inc.

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

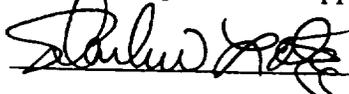
The undersigned declares that the above stated United States Patent Number 5,442,049 covers the composition, formulation and/or method of use of Fomivirsen (name of drug product). This product is:

X currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:



(Mark W. Lotz, R.Ph.)

Date:

6 April 1998

Title (optional):

Executive Director, Regulatory Affairs

Telephone Number (optional):

(760) 603-2378

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*, a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Location address: (For FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301) 594-6463

- Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information, please refer to 21 C.F.R. § 314.53.

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53

for

NDA # 20-961

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

X Trade Name: VitraveneTM
X Active Ingredient(s) Fomivirsen sodium
X Strength(s): 6.6 mg / mL
X Dosage Form: Injection
X Approval Date: (to be determined)

A. This section should be completed for each individual patent

U.S. Patent Number: 5,595,978

Expiration Date: August 15, 2012

Type of Patent-Indicate all that apply:

X Drug Substance (Active Ingredient) Y X N
X Drug Product (Composition/Formulation) X Y N
X Method of Use X Y N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

The method for which approval is being sought is treatment of cytomegalovirus (CMV) retinitis in a human patient by intravitreal administration of a phosphorothioate oligonucleotide which is capable of hybridizing with CMV mRNA.

Name of Patent Owner: Isis Pharmaceuticals, Inc.

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

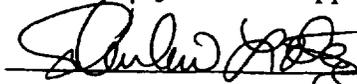
The undersigned declares that the above stated United States Patent Number 5,595,978 covers the composition, formulation and/or method of use of Fomivirsen (name of drug product). This product is:

X currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

X the subject of this application for which approval is being sought.

Signed:



(Mark W. Lotz, R.Ph.)

Date:

6 April 1998

Title (optional):

Executive Director, Regulatory Affairs

Telephone Number (optional):

(760) 603-2378

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,^o a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

Location address: (For FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301) 594-6463

^o - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.



**ISIS
PHARMACEUTICALS**

REQUEST FOR CLAIMED EXCLUSIVITY

Pursuant to Sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the Federal Food, Drug, and Cosmetic Act and 21CFR314.50(j) and 314.108(b)(2), Isis Pharmaceuticals, Inc. hereby requests five years marketing exclusivity for Vitravene™ Injection (fomivirsen sodium intravitreal injection). The New Drug Application, NDA 20-961, contains an active moiety in the drug product that, to the best knowledge and belief of Isis Pharmaceuticals, has not been previously approved under Section 505(b) of the Act.



Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs

50 MARCH 1998
Date

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 20-961 SUPPL # _____

Trade Name Vitrovene Injection Generic Name Fomivirsen sodium intrathecal injection

Applicant Name Isis Pharmaceuticals HFD- 550

Approval Date, if known 8/26/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES // NO /___/

b) Is it an effectiveness supplement? YES /___/ NO //

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES // NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES // NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
Investigation #2	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature: /S/
Title: _____

 8/26/98
Date

 /S/

Signature of Division Director

_____ Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

Complete for all original applications and an efficacy supplements

NDA # NDA 20-961 Applicant: Isis Pharmaceuticals
Supplement #
Therapeutic Class 1P
Circle one: SE1 SE2 SE3 SE4 SE5 SE6
Action: AP (AE) NA
HFD-550

Trade (generic) name/dosage form: Vitravene (formivirsen sodium intravitreal injectable) Injection

Applicant Indication(s) previously approved: N/A

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application: for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) who are intolerant of another treatment for CMV retinitis or who were insufficiently responsive to a previous treatment for CMV retinitis.

(For supplements, answer the following questions in relation to the proposed indication.)

1. PEDIATRIC LABELING IS ADEQUATE. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

2. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

b. The applicant has committed to doing such studies as will be required.

- (1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, explain the status on the back of this form.

c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain why pediatric studies are not needed.: The indication is not common in children.

4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Handwritten signature: /S/ [initials] CSO
Signature of Preparer and Title (PM, CSO, MO, other)

August 7, 1998
Date

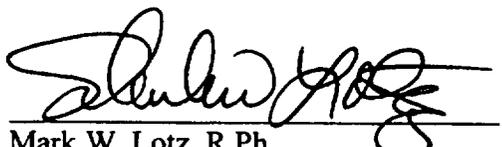
cc: Original NDA 20-961
HFD-550/DIV File
NDA Action Package
HFD-510 G.Troendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
5/95


**ISIS
PHARMACEUTICALS**

DEBARMENT CERTIFICATION STATEMENT

As required under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act, Isis Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) of the Act in connection with the New Drug Application for Vitravene™ Injection (fomivirsen sodium intravitreal injection), NDA 20-961.



Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs

30 MARCH 1998
Date

**APPEARS THIS WAY
ON ORIGINAL**

consult to Rao

ISIS
PHARMACEUTICALS

NC
NEW CORRESP
TRIPICODIC

March 31, 1998

Wiley A. Chambers, M.D.
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA Amendment to Pre-NDA Submission of Chemistry, Manufacturing, and Controls Data

Dear Dr. Chambers:

Isis Pharmaceuticals hereby submits five corrected pages for the Pre-NDA Submission of the Chemistry, Manufacturing, and Controls Data. The enclosed pages are page numbers 120 and 128-131 of Volume 3. In the March 24, 1998 submission, the cross reference numbers (inserted by an electronic software publishing system) did not print on these pages and appeared as "unreconciled". Three copies of the corrected pages are included in this submission.

If you have any questions regarding this submission, please contact me at (760) 603-2565 or Mark Lotz at (760) 603-2378.

Sincerely,

Sally A. Barr

Sally A. Barr
Manager, Regulatory Affairs



**ISIS
PHARMACEUTICALS**

Mark W. Lotz, R.Ph.
Executive Director
Regulatory Affairs
Internet: mlotz@isisph.com

April 6, 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

ATTN: Wiley A. Chambers, M.D.
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
HFD-550

RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA 20-961

Dear Dr. Chambers,

Isis Pharmaceuticals hereby submits a New Drug Application for Vitravene™ Injection (fomivirsen sodium intravitreal injection) under the provisions of 21CFR314.50 and Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Included in this submission is one complete archival copy (Volumes 2.1 through 2.366) and a technical review copy. Volumes 2.140 – 2.204 are not included as these are fundus photographs and are being submitted under separate cover directly to the Division, as requested. They will be jacketed in blue archival jackets and labeled appropriately.

The pagination and cross-referencing for the application follows a similar format. The pagination is by Section, Volume, and Page. Cross-referencing within the text is done in a similar fashion, contained within brackets, e.g., “[05-001-100]” would be Section 5, Volume 1, Page 100; “[08-010-90]” would be Section 8, Volume 10, Page 90.

Also included are seven review copies of the Summary Volume; one for each of the six technical reviewers and one additional for Chemistry for the consulting reviewer. In addition, ten desk copies of the Summary Volume have been forwarded under separate cover to Ms. Lori Gorski, of the Agency, as per the Division’s request. A CD-ROM, containing this application in PDF format (provided as a review aid), will also be

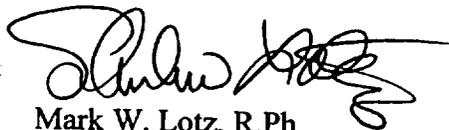
provided to Dr. Chambers. The electronic version of the application on the CD-ROM is identical to the paper copy provided in this submission.

Please note that Section 4, Chemistry, Manufacturing, and Controls, is contained in Volumes 1.1 through 1.10 of the Pre-NDA Submission dated March 24, 1998. Isis certifies that a true copy of the Chemistry, Manufacturing, and Controls section is being sent to the Los Angeles District of the U.S. Food and Drug Administration to the attention of Ms. Kim Childress. The Analytical Methods Validation Package will be submitted to the Agency upon request.

As the pediatric population in this disease state, cytomegalovirus retinitis, is not sufficiently large to do adequate clinical trials, information regarding the use of this new drug in this population is not included in this application. The appropriate statement is included in the draft package insert regarding the use of Vitravene™ in pediatric patients.

We trust this application is complete. If you have any questions, please contact me at (760) 603-2378 or Sally Barr at (760) 603-2565.

Sincerely,



Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

▲
ISIS
PHARMACEUTICALS

Desk Copy

April 9, 1998

Wiley A. Chambers, M.D.
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

Isis Pharmaceuticals hereby submits the New Drug Application for Vitravene™ Injection (fomivirsen sodium intravitreal injection) in electronic format. This submission is a **Review Aid Only, Not an Archival Copy**. This electronic version of the application is identical to the paper version of the New Drug Application.

Five CD-ROMs containing Volumes 2.1 through 2.366 (excluding volumes 2.140 - 2.204, fundus photographs) are being provided in PDF format. An additional CD-ROM named "PDF Viewer Tools" and a CD-ROM containing the Pre-NDA submission of Chemistry, Manufacturing, and Controls Data have previously been provided to Ms. Lori Gorski, of the Agency. In order to view, copy, and paste from the PDF files, Acrobat Exchange 3.01 needs to be installed on the local machine.

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Handwritten signature of Sally A. Barr in cursive.

Sally A. Barr
Manager, Regulatory Affairs

SB:mt

HFD-350 Gorski

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 22 1998

NDA 20-961

Isis Pharmaceuticals, Inc.
Attention: Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Mr. Lotz:

We received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Vitravene Injection (fomivirsen sodium intravitreal injection)
Therapeutic Classification: Priority
Date of Application: April 6, 1998
Date of Receipt: April 9, 1998
Our Reference Number: NDA 20-961

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 8, 1998, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Lori Gorski, Project Manager, at (301) 827-2090.

Please site the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely



4/22/98

Chin Koerner, M.S.
Acting Supervisory Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Trina

ISIS
PHARMACEUTICALS

NC
NEW CORRESP
ORIGINAL

April 23, 1998

Ms. Veneeta Tandon
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Room N227
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

Dear Ms. Tandon:

Isis Pharmaceuticals hereby submits one desk copy of ISIS 2922-CS5, An Open-Label Pharmacokinetic (PK) Study of Intravitreal ISIS 2922 in AIDS Patients with Cytomegalovirus Retinitis (CMVR), as requested by Ms. Lori Gorski of the Agency. This copy is identical to Volume 2.20 of the NDA submission to the Agency.

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Sally A. Barr
Manager, Regulatory Affairs

SB/mt

▲
ISIS
PHARMACEUTICALS

DUPLICATE
NDA ORIG AMENDMENT

Mark W. Lotz, R.Ph.
Executive Director
Regulatory Affairs
Internet: mlotz@isisph.com

BP

April 30, 1998

Wiley A. Chambers, M.D.
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers,

Pursuant to the telephone conference of April 29, 1998 between Isis Pharmaceuticals and the Agency, the following information regarding the preclinical safety studies and the clinical study program is provided for the Agency's review.

Preclinical Safety

Isis Pharmaceuticals hereby requests a waiver from performing 6-Month Repeat-Dose Intravitreal Toxicity Studies based on the technical limitation of repeated intravitreal injection for long periods of time in laboratory animals, and the requirement of prophylactic subconjunctival corticosteroids in chronic treatment studies. The requirement for prophylactic corticosteroid treatment in animals is not representative of the tolerability of fomivirsen in patients. The existing three month studies have provided a characterization of the local tolerability of fomivirsen and, in fact, may represent a worst case response to treatment. Further long-term in a small number of primates would not provide any additional useful information.

A waiver from performing carcinogenicity studies for fomivirsen is also requested. Considering the lack of meaningful systemic exposure to fomivirsen following intravitreal administration of clinically relevant doses, conducting further systemic



toxicity studies is not considered relevant to the safety assessment of this compound for the intended use.

In addition, a waiver from performing fertility studies is requested on the basis of absence of histologic changes in testes after 2 weeks of intravenous dosing with up to 50 mg/kg every other day (Study No. ISIS 2922-AS02). Data from other phosphorothioate oligonucleotides indicate that there is little or no exposure of the testes to intact oligonucleotide and no histologic changes in the testes of mice or primates after 6 months of dosing by subcutaneous injection. Segment I/II studies with other related phosphorothioate oligonucleotides indicated no alterations in fertility or reproductive performance in mice (Study No. ISIS 2302-AS18).

With regard to teratology testing, Isis is requesting a deferral from performing this study contingent on approval of fomivirsen injection. Should fomivirsen be approved, a teratology study would be performed allowing reasonable time for scheduling and preparation of material for this study, which should take approximately 6 months. This teratology study would be conducted in rabbits using typical design for Segment II studies including the intravenous route of administration (to maximize systemic exposure) and a top dose sufficient to produce minimal maternal toxicity.

Clinical Study Program

Based on the conversation between Isis and the Agency in the April 29th telephone conference, Isis is evaluating the over-all clinical study program to assure maximal patient enrollment. The information requested by the Agency (time-table for completion of studies, submittal of reports, etc.) will be submitted as soon as this evaluation is complete, most probably within the next 7 days.

We trust this information is adequate. If you have any questions regarding this information, please do not hesitate to give me a call.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark W. Lotz".

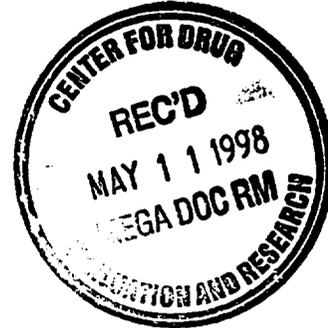
Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs

▲
**ISIS
PHARMACEUTICALS**

BC
ORIGINAL AMENDMENT
TRIP!

May 8, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

Isis Pharmaceuticals hereby submits information supporting a request for deferral of certain drug product validation data.

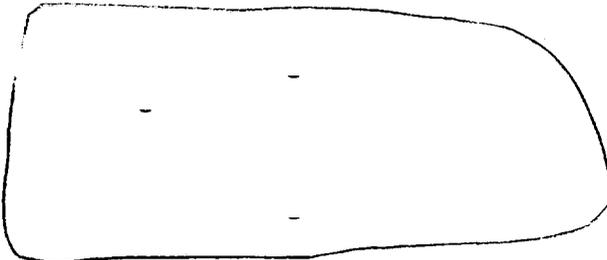
If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Sally A. Barr
Manager, Regulatory Affairs

SB:mt

cc:



ISIS
PHARMACEUTICALS

BC

May 18, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

Isis Pharmaceuticals hereby submits information supporting a request for a 36-month expiry date for the drug product.

Information contained in the Pre-NDA Submission, dated March 24, 1998, supported a 24-month expiry date. The appended stability update provides additional information that supports a 36-month expiry date for the drug product.

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Handwritten signature of Sally A. Barr in cursive.

Sally A. Barr
Manager, Regulatory Affairs

SB:mt

▲
**ISIS
PHARMACEUTICALS**

Mark W. Lotz, R.Ph.
Executive Director
Regulatory Affairs
Internet: mlotz@isisph.com

June 3, 1998

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA Amendment

Dear Dr. Chambers:

A discussion was held on May 29, 1998 between Ms. Lori Gorski, of the Agency, and Ms. Sally Barr and Mr. Mark Lotz, of Isis Pharmaceuticals, regarding the information provided by Isis in an April 30, 1998 NDA Amendment. In the Amendment, Isis requested a waiver from performing carcinogenicity studies and a 6-month repeat dose tox study, and committed to performing a Segment II teratology study in rabbits.

The Agency, in the May 29, 1998 discussion, requested additional clarification of the Segment II study in regard to timing of initiation of the study.

The Segment II study is scheduled to start on or before August 10, 1998. The in-life portion of the study will be approximately 30 days, followed by sample and tissue analysis. It is anticipated that the draft report for the study will be completed by December 20, 1998. A final report will be available January 20, 1999.

An outline of the study is appended. The study will be conducted by the intravenous route of administration in order to attain the systemic exposure and maternal toxicity necessary to adequately address the potential effects on fetal development.



We trust this information is adequate for the Agency's request.

If you have any questions, please do not hesitate to give me a call.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark W. Lotz".

Mark W. Lotz, R.Ph.
Executive Director, Regulatory Affairs

MWL:tj

**APPEARS THIS WAY
ON ORIGINAL**

▲
**ISIS
PHARMACEUTICALS**

B2
ORIG AMENDMENT

ORIGINAL

June 29, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

Pursuant to a request made by Ms. Lori Gorski of the Agency, Isis Pharmaceuticals hereby submits the background information package for the participants in the upcoming Ophthalmic Advisory Committee Meeting on July 22, 1998 as an NDA Amendment.

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Sally A. Barr
Manager, Regulatory Affairs

SB:mt

▲
**ISIS
PHARMACEUTICALS**

July 30, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

In a July 30, 1998 telephone discussion with Isis Pharmaceuticals, Dr. Rao Kambhampati, of the Agency, requested additional information on the experimental procedure for [redacted] used in each batch of [redacted] or, alternately, an executed batch record for one batch of [redacted]

Appended is an executed batch record for [redacted] 0045, which provides the requested information.

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,


Sally A. Barr
Manager, Regulatory Affairs

SB:mt



ISIS
PHARMACEUTICALS

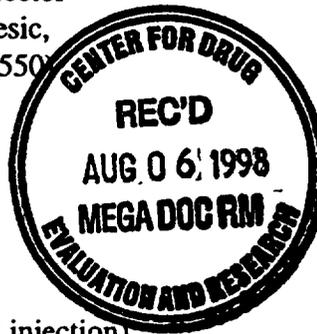
BC

ORIG AMENDMENT

Tripl:

August 4, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

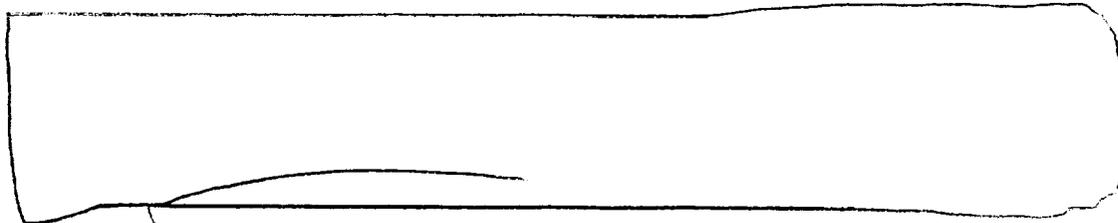


RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

In support of the proposed revision of release specifications for the active pharmaceutical ingredient (submitted as an NDA Amendment dated July 29, 1998), the following changes to the in-process parameters have also been made. These changes should be incorporated in the CMC Pre-NDA submission.



The reference to "and bacterial endotoxin" should be removed from the flowchart (refer to Sec. 04, Vol. 001, P. 048 of the CMC Pre-NDA submission) since this was a typographical error. Appended as Exhibit I is a revised flowchart.

If you have any questions regarding this information, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

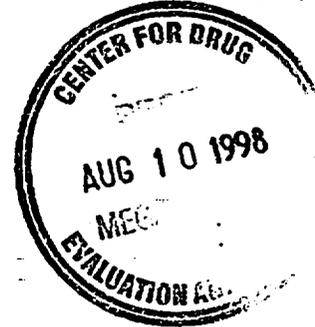
Sally A. Barr
Manager, Regulatory Affairs

▲
**ISIS
PHARMACEUTICALS**

DC
ORIG AMENDMENT

ORIGINAL

August 7, 1998



Wiley A. Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

Isis Pharmaceuticals hereby submits the Analytical Methods Validation Package under the provisions of 21 CFR 314.50 and Section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act.

The District testing laboratories should be advised that if the [redacted] is performed, the [redacted] should be [redacted]

If you have any questions regarding this submission, please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

Sally A. Barr

Sally A. Barr
Manager, Regulatory Affairs

SB:mt

▲
**ISIS
PHARMACEUTICALS**

August 12, 1998

Wiley A. Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

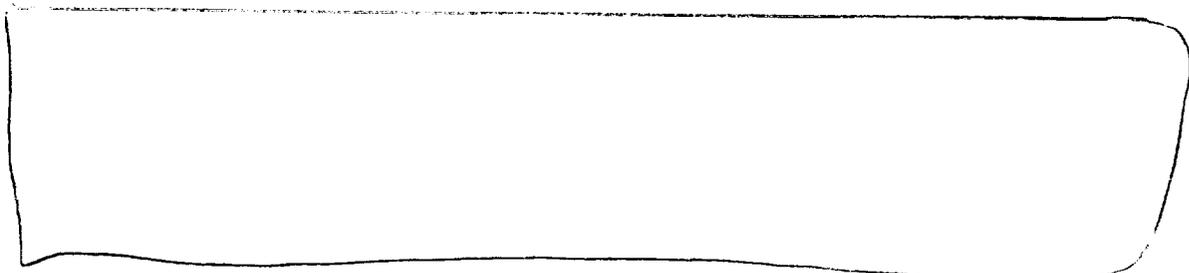
RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

NDA AMENDMENT

Dear Dr. Chambers:

In an August 6, 1998 meeting at Isis Pharmaceuticals, Dr. Su Tso, of the Agency, requested information related to the chemistry, manufacturing and controls of the new drug.

The following is provided:



Please note that the information contained in Exhibits I and II was previously submitted in an NDA Amendment dated July 29, 1998.

We trust this information satisfies the Agency's request. If you have any questions please contact Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,


Sally A. Barr
Manager, Regulatory Affairs

▲
**ISIS
PHARMACEUTICALS**

August 14, 1998

nc
DUPLICATE



Wiley A. Chambers, M.D., Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products (HFD-550)
Document Control Room, N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: Vitravene™ Injection
(fomivirsen sodium intravitreal injection)
NDA No. 20-961

General Correspondence

Dear Dr. Chambers:

Isis Pharmaceuticals will be attending a meeting with the Agency on August 24, 1998, at 11:00 AM. Appended is a listing of the attendees for Isis. Isis understands that the Agency is planning to utilize the August 7, 1998 NDA Amendment (excluding the Exhibits III, IV, and V) as the meeting package.

If you have any questions, please do not hesitate to call Mark Lotz at (760) 603-2378 or me at (760) 603-2565.

Sincerely,

A handwritten signature in cursive that reads "Sally A. Barr".

Sally A. Barr
Manager, Regulatory Affairs

SB:mt