CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040745

CHEMISTRY REVIEWS

ANDA 40-745

CYCLOPHOSPHAMIDE FOR INJECTION USP, 500 MG/VIAL, 1.0 G/VIAL, AND 2.0 G/VIAL

BAXTER HEALTHCARE CORPORATION

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 40-745

2. **REVIEW #:** 1

3. **REVIEW DATE:** 19-JUL-2006

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:** None

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

Submission(s) Reviewed	Document Date
Original ANDA	31-JAN-2006
Acceptable for filing	01-FEB-2006

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

Name: Baxter Healthcare Corporation Anesthesia & Critical Care
Address: 2 Esterbrook Lane Cherry Hill,
New Jersey 08003-4099

Representative: Sandra P. Bobila
Telephone: 856-489-2197

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name N/A
   b) Non-Proprietary Name (USAN) CYCLOPHOSPHAMIDE FOR INJECTION, USP

9. **LEGAL BASIS FOR SUBMISSION:**

Ref Listed Drug: CYTOXAN
Firm: BRISTOL-MYERS SQUIBB NDA#: 12-142

10. **PHARMACOL. CATEGORY:** CYTOXIC ALKYLATING AGENT

11. **DOSAGE FORM:** Lyophilized powder:

12. **STRENGTH/POTENCY:** 500 mg/vial, 1 g/vial, and 2 g/vial

13. **ROUTE OF ADMINISTRATION:** Intravenous, intramuscular, intraperitoneal, or intrapleural injection or intravenous infusion

14. **Rx/OTC DISPENSED: __x_Rx ___OTC**

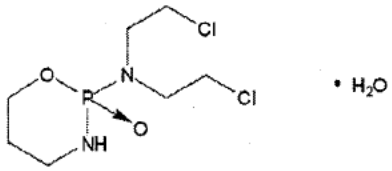
15 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) No**
(If applicable, fill out the form for special products and deliver to the team leader).

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

Molecular Weight: 279.10
Molecular Formula: $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Chemical Name: N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide

Additional Names: 1-bis(2-chloroethyl)amino-1-oxo-2-aza-5-oxaphosphoridin monohydrate ; bis(2-phosphamide cyclic propanolamide ester monohydrate; N,N-bis(ß-chloroethyl)-N',O-propylenephosphoric acid ester diamide monohydrate; cyclophosphane; cytophosphane



17. **RELATED/SUPPORTING DOCUMENTS:**
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4			(b) (4)
	III			4			

(b) (4)	III	(b) (4)		4			(b) (4)
	III			4			
	III			4			
3594	II	Baxter Oncology GmbH	Cyclophosphamide	1	Adequate	7/26/06	Drug Substance

[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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	3/30/06	S. Adams
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Waiver granted	06/06/06	D. Conner
EA	Acceptable	07/20/06	J. Wetzel
Radiopharmaceutical	N/A		
Other	N/A		

19. **ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt. _x___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 40-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 40-745 is not approvable for the following reasons:
There are deficiencies in the CMC portion of the application.
Labeling Review is pending.
Micro Review is pending.

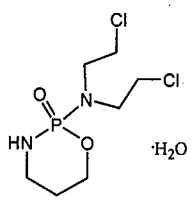
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2- chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



Cyclophosphamide

Drug Product
Cyclophosphamide for injection, a powder, is a nitrogen mustard alkylating agent, used to treat various types of cancer and some autoimmune disorders. It is a prodrug and is converted in the liver to active forms that have chemotherapeutic activity.

At first, it is converted by the liver into acrolein and phosphoramide. Acrolein and phosphoramide are the active compounds, and they slow the growth of cancer cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cancerous cells. Therefore, it is referred to as a cytotoxic drug. Unfortunately, normal cells also are affected, and this results in serious side effects. Cyclophosphamide also suppresses the immune system and is also referred to as immunosuppressive.

The powder should be stored at (b) (4). Solutions prepared with bacteriostatic water are usable up to 24 hours if stored at room temperature and up to 6 days if stored in the refrigerator.

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

Mode of Action
Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5% to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

Proposed Clinical Use

CYCLOPHOSPHAMIDE FOR INJECTION is indicated for the following: Malignant Diseases;
Malignant lymphomas
Multiple myeloma
Leukemias
Mycosis fungoides
Neuroblastoma
Adenocarcinoma of the ovary
Retinoblastoma

Carcinoma of the breast
Nonmalignant Disease: Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

Proposed Dosage and Administration

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly. Hence, the MDD may be considered to be (b) (4)

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

ANDA 40-745 is not approvable for the following reasons:
There are deficiencies in the CMC portion of the application.
Labeling Review is pending.
Micro Review is pending.

III. Administrative

A. Reviewer's Signature

Joseph R. Wetzel

B. Endorsement Block

Joseph R. Wetzel, Review Chemist/07/26/06 revised

J. Fan, Team Leader/07/26/06 revised
R. Adigun, Project Mgr./ 07/26/06 revised

C. CC Block

ANDA40-745
DIV FILE
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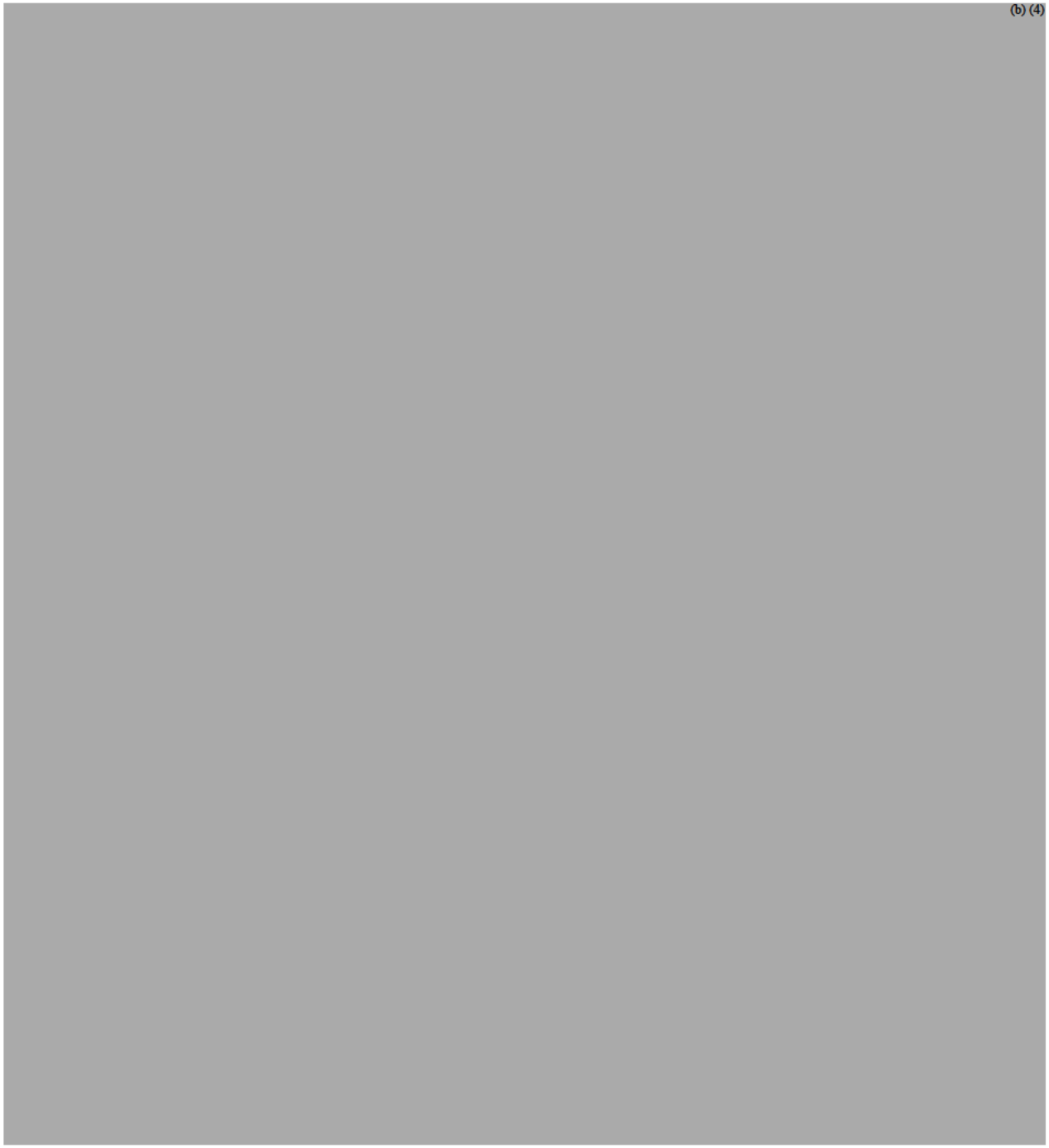
Chemistry Assessment

20. COMPONENTS AND COMPOSITION Not Satisfactory

(b) (4)

[redacted]

Following this page, 17 pages withheld in full (b)(4)



30. MICROBIOLOGY

Review status: pending

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The drug substance and the drug product are USP compendial items.
Method validation is not necessary.

32. LABELING

Review status: pending

33. ESTABLISHMENT INSPECTION

Acceptable per S. Adams, 3/30/06.

34. BIOEQUIVALENCY STATUS

Waiver granted, 06/06/06, per D. Conner.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: **Granted per J. Wetzel 7/15/06**

Pursuant to 21 CFR 25.31 (a) Baxter Healthcare Corp., requests a categorical exclusion from the requirement of an environment assessment, since Cyclophosphamide for Injection does not increase the use of the active moiety from the currently marketed version of this product. The firm certifies compliance with all applicable city, county, state and federal environmental rules and regulations.

36. Chemistry Comments to be Provided to the Applicant

ANDA:40-745 APPLICANT: Baxter Healthcare Corporation

DRUG PRODUCT: Cyclophosphamide for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Please calculate and provide the MDD for the drug substance.

2. (b) (4)

3.

4.

5.

6.

7.

8.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The current USP methods are the regulatory methods and results from these methods shall rule in the event of a dispute.

2. Please provide all available long-term stability data.

3. Information related to sterility assurance and labeling are pending review. After the reviews are complete, any deficiencies found will be communicated to you under separate cover(s).

4. Expiration dating is limited to 24 months based on the data provided. However, the expiration period may be extended with the post approval submission of satisfactory CRT stability data from at least three commercial production batches.

Sincerely yours,

9/21/06

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-745

DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625 /Joseph R. Wetzel, Review Chemist /07/26/06 revised Joseph R Wetzel 9/8/06
HFD-625/ J. Fan, Team Leader/07/26/06 revised 9/14/06
HFD-617/R. Adigun, Project Manager/07/26/06 revised 9/14/06

F/T:
\\Cdsnas\OGDS11\FIRMSAM\BAXTER\LTRS&REV\40745 REV1 jrw.doc

ANDA 40-745

CYCLOPHOSPHAMIDE FOR INJECTION USP, 500 MG/VIAL, 1.0 G/VIAL, AND 2.0 G/VIAL

BAXTER HEALTHCARE CORPORATION

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 40-745

2. **REVIEW #:** 2

3. **REVIEW DATE:** 30-JUN-2007

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:** None

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

Submission(s) Reviewed	**Document Date**
Original ANDA	31-JAN-2006
Acceptable for filing	01-FEB-2006
Amendment	09-FEB-2007
Amendment	04-JUN-2007

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

.

Name: Baxter Healthcare Corporation Anesthesia & Critical Care
Address: 2 Esterbrook Lane
Cherry Hill, NJ 08003

Representative: Sandra P. Bobila
Telephone: 856-489-2197

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name N/A
   b) Non-Proprietary Name (USAN) CYCLOPHOSPHAMIDE FOR INJECTION, USP

9. **LEGAL BASIS FOR SUBMISSION:**

Ref Listed Drug: CYTOXAN
Firm: BRISTOL-MYERS SQUIBB NDA#: 12-142

10. **PHARMACOL. CATEGORY:** CYTOXIC ALKYLATING AGENT

11. **DOSAGE FORM:** Lyophilized powder:

12. **STRENGTH/POTENCY:** 500 mg/vial, 1 g/vial, and 2 g/vial

13. **ROUTE OF ADMINISTRATION:** Intravenous, intramuscular, intraperitoneal, or intrapleural injection or intravenous infusion

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

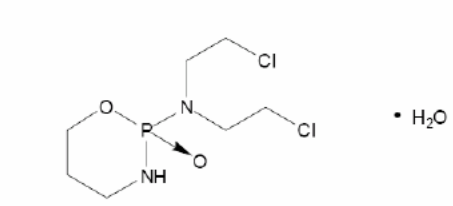
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)** **No**

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

Molecular Weight: 279.10
Molecular Formula: $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Chemical Name: N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide

Additional Names: 1-bis(2-chloroethyl)amino-1-oxo-2-aza-5-oxaphosphoridin monohydrate ; bis(2-phosphamide cyclic propanolamide ester monohydrate; N,N-bis(ß-chloroethyl)-N',O-propylenephosphoric acid ester diamide monohydrate; cyclophosphane; cytophosphane



17. **RELATED/SUPPORTING DOCUMENTS:**
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
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	III			4			

(b) (4)	III	(b) (4)		4			(b) (4)
	III			4			
	III			4			
3594	II	Baxter Oncology GmbH	Cyclophosphamide	1	Adequate	9/1/06	Drug Substance

[1] Action codes for DMF Table:

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

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

B. Other Documents:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	3/30/06	S. Adams
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Acceptable	6/6/06	B. Fabian-Fritsch
EA	Acceptable	07/20/06	J. Wetzel
Radiopharmaceutical	N/A		
Other	N/A		

19. **ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt. _x___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 40-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the application.
The Labeling is pending review.
Micro Review is pending.

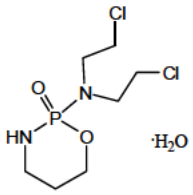
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

Drug Substance
Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2- chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



Cyclophosphamide

Drug Product
Cyclophosphamide for injection, a powder, is a nitrogen mustard alkylating agent, used to treat various types of cancer and some autoimmune disorders. It is a prodrug and is converted in the liver to active forms that have chemotherapeutic activity.

At first, it is converted by the liver into acrolein and phosphoramide. Acrolein and phosphoramide are the active compounds, and they slow the growth of cancer cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cancerous cells. Therefore, it is referred to as a cytotoxic drug. Unfortunately, normal cells also are affected, and this results in serious side effects. Cyclophosphamide also suppresses the immune system and is also referred to as immunosuppressive.

The powder should be stored at (b) (4) Solutions prepared with bacteriostatic water are usable up to 24 hours if stored at room temperature and up to 6 days if stored in the refrigerator.

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

Mode of Action
Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5% to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

Proposed Clinical Use

CYCLOPHOSPHAMIDE FOR INJECTION is indicated for the following:
Malignant Diseases;
Malignant lymphomas
Multiple myeloma
Leukemias
Mycosis fungoides
Neuroblastoma
Adenocarcinoma of the ovary
Retinoblastoma
Carcinoma of the breast

Nonmalignant Disease: Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

Proposed Dosage and Administration

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly. Hence, the MDD may be considered to be 1750 mg.

Deficiency:

- Please calculate and provide the MDD for the drug substance.

Firm's Response

We have calculated the Maximum Daily Dose (MDD) of cyclophosphamide drug substance administered per day in accordance to the dosage and administration indicated in the package insert for CYTOXAN° (cyclophosphamide for injection, USP) reference listed drug. There is no excipient in the drug product formulation. Therefore, the MDD of cyclophosphamide drug substance is 25 mg/kg/day or 1.75 g/day for a patient with body weight of 70 kg. Please refer to Attachment 1 for details regarding the calculation of the MDD.

Cyclophosphamide is a synthetic antineoplastic drug used as a chemotherapeutic agent for the treatment of numerous malignancies including lymphomas, myelomas, leukemias, carcinomas and others. The dosing of cyclophosphamide will vary according to patient condition, weight, and diagnosis. Standard intravenous dosing regimens are in the range of 1-15 mg/kg/day up to 50 mg/kg divided over 2 days (Ref 1). Therefore, the maximum daily (approved) dose of the drug substance is 25 mg/kg/day or 1.75g/day (50 mg/kg 2 days=25 mg/kg/day x 70kg=1.75 g/day).

References

1. Cytoxan (Cyclophosphamide for Injection, USP). Bristol Myers Squibb. H4-B0001-06- 04. Revised November, 2003.

C. Basis for Approvability or Not-Approval Recommendation

This ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the application.
The Labeling was found to be inadequate.
Micro Review is pending.

Following this page, 14 pages withheld in full (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY
Review status: pending

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
The drug substance and the drug product are USP compendial items.
Method validation is not necessary.

32. LABELING Pending
Firm responded labeling deficiencies on 7/18/07. Labeling review is pending.

33. ESTABLISHMENT INSPECTION
Acceptable per S. Adams, 3/30/06.

34. BIOEQUIVALENCY STATUS

Waiver granted, 06/06/06, per D. Conner.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Granted per J. Wetzel 7/15/06
Pursuant to 21 CFR 25.31 (a) Baxter Healthcare Corp., requests a categorical exclusion from the requirement of an environment assessment, since Cyclophosphamide for Injection does not increase the use of the active moiety from the currently marketed version of this product.
The firm certifies compliance with all applicable city, county, state and federal environmental rules and regulations.

36. Chemistry Comments to be Provided to the Applicant

ANDA:40-745 APPLICANT: Baxter Healthcare Corporation

DRUG PRODUCT: Cyclophosphamide for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Please use the appropriate significant figures in the drug substance and drug product release specifications.

2. (b) (4)

3.

4.

5.

6. Please submit updated stability data sheets with all the above revisions.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-745

DIV FILE
Field Copy

Endorsements :

HFD-625 /Joseph R. Wetzel, Review Chemist /06/30/07
HFD-625/ J. Fan, Team Leader/06/30/07
HFD-617/R. Adigun, Project Manager/06/30/07

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Minor

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

/s/

Joseph Wetzel
8/8/2007 10:11:00 PM
CHEMIST

Rosalyn Adigun
8/27/2007 03:00:28 PM
CSO

James Fan
9/4/2007 05:26:39 PM
CHEMIST

ANDA 40-745

CYCLOPHOSPHAMIDE FOR INJECTION USP, 500 MG/VIAL, 1.0 G/VIAL, AND 2.0 G/VIAL

BAXTER HEALTHCARE CORPORATION

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA #** 40-745

2. **REVIEW #:** 3

3. **REVIEW DATE:**22-JAN-2008

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:**

Original ANDA	31-JAN-2006
Acceptable for filing	01-FEB-2006
Amendment	09-FEB-2007
Amendment	04-JUN-2007

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

Submission(s) Reviewed	**Document Date**
Amendment	11-OCT-2007

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

Name: Baxter Healthcare Corporation Anesthesia & Critical Care
Address: 2 Esterbrook Lane
Cherry Hill, NJ 08003

Representative: Sandra P. Bobila
Telephone: 856-489-2197

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name N/A
   b) Non-Proprietary Name (USAN) CYCLOPHOSPHAMIDE FOR INJECTION, USP

9. **LEGAL BASIS FOR SUBMISSION:**

Ref Listed Drug: CYTOXAN
Firm: BRISTOL-MYERS SQUIBB NDA#: 12-142

10. **PHARMACOL. CATEGORY:** CYTOXIC ALKYLATING AGENT

11. **DOSAGE FORM:** Lyophilized powder:

12. **STRENGTH/POTENCY:** 500 mg/vial, 1 g/vial, and 2 g/vial

13. **ROUTE OF ADMINISTRATION:** Intravenous, intramuscular, intraperitoneal, or intrapleural injection or intravenous infusion

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

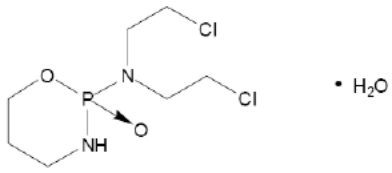
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)** **No**

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

Molecular Weight: 279.10
Molecular Formula: $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Chemical Name: N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide

Additional Names: 1-bis(2-chloroethyl)amino-1-oxo-2-aza-5-oxaphosphoridin monohydrate ; bis(2-phosphamide cyclic propanolamide ester monohydrate; N,N-bis(ß-chloroethyl)-N',O-propylenephosphoric acid ester diamide monohydrate; cyclophosphane; cytophosphane



17. **RELATED/SUPPORTING DOCUMENTS:**
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	50 mL Vial	4			(b) (4)
	III		75 mL Vial	4			

(b) (4)	III	(b) (4)		4			(b) (4)
	III			4			
	III			4			
3594	II	Baxter Oncology GmbH	Cyclophosphamide	1	Adequate	1/31/08	Drug Substance

[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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/13/06	G. Arhin
EES	Acceptable	3/30/06	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	11/6/07	A. Payne
Bioequivalence	Acceptable	6/6/06	B. Fabian-Fritsch
EA	Acceptable	7/20/06	J. Wetzel
Radiopharmaceutical	N/A		
Other	N/A		

19. **ORDER OF REVIEW**

The application submission(s) covered by this review was taken in the date order of receipt. _x___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 40-745

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is approvable.

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

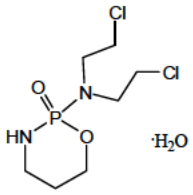
N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2- chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



Cyclophosphamide

Drug Product

Cyclophosphamide for injection, a powder, is a nitrogen mustard alkylating agent, used to treat various types of cancer and some autoimmune disorders. It is a prodrug and is converted in the liver to active forms that have chemotherapeutic activity.

At first, it is converted by the liver into acrolein and phosphoramide. Acrolein and phosphoramide are the active compounds, and they slow the growth of cancer cells by interfering with the actions of deoxyribonucleic acid (DNA) within the cancerous cells. Therefore, it is referred to as a cytotoxic drug. Unfortunately, normal cells also are affected, and this results in serious side effects. Cyclophosphamide also suppresses the immune system and is also referred to as immunosuppressive.

The powder should be stored at (b) (4) Solutions prepared with bacteriostatic water are usable up to 24 hours if stored at room temperature and up to 6 days if stored in the refrigerator.

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

Mode of Action
Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5% to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

Proposed Clinical Use

CYCLOPHOSPHAMIDE FOR INJECTION is indicated for the following:
Malignant Diseases;
Malignant lymphomas
Multiple myeloma
Leukemias
Mycosis fungoides
Neuroblastoma
Adenocarcinoma of the ovary
Retinoblastoma
Carcinoma of the breast
Nonmalignant Disease: Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

Proposed Dosage and Administration

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period

of 2 to 5 days. Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly. Hence, the MDD may be considered to be 1750 mg (*1.75 g/day)*.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

Following this page, 11 pages withheld in full (b)(4)

(b) (4)

[redacted]

30. MICROBIOLOGY
Review status: Acceptable on May 13, 2008 by G. Arhin

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
The drug substance and the drug product are USP compendial items.
Method validation is not necessary.

32. **LABELING**
Labeling status: Acceptable on November 6, 2007 by A. Payne

33. ESTABLISHMENT INSPECTION

Acceptable per S. Adams, on March 30, 2006

34. BIOEQUIVALENCY STATUS

Waiver granted on June 6, 2006 by B. Fritsch

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Pursuant to 21 CFR 25.31 (a) Baxter Healthcare Corp., requests a categorical exclusion from the requirement of an environment assessment, since Cyclophosphamide for Injection does not increase the use of the active moiety from the currently marketed version of this product.
The firm certifies compliance with all applicable city, county, state and federal environmental rules and regulations.

cc: ANDA 40-745

DIV FILE
Field Copy

Endorsements :

HFD-625 /Joseph R. Wetzel, Review Chemist /01/22/08
HFD-625/ J. Fan, Team Leader/01/22/08
HFD-617/R. Adigun, Project Manager/01/22/08

F/T:
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/s/

Joseph Wetzel
5/22/2008 07:40:09 PM
CHEMIST

Rosalyn Adigun
5/27/2008 09:25:56 AM
CSO

James Fan
5/28/2008 09:22:19 AM
CHEMIST