CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-678/S003

CORRESPONDENCE

Exclusivity Checklist

NDA: 20-678/S-003				
Trade Name: Clinimix E™ sulfite free				
Generic Name: Amino Acid with Electrolytes in Dextrose with Calcium				
Applicant Name: Baxter Healthcare				
Division: DMEDP (HFD-510)				
Project Manager: Steve McCort				
Approval Date:				
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 questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE8			
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	X	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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes		No	X
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	Yes		No	

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.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product.				
NDA #				
2. Combination product.	Yes	X	No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product Travasol-sulfite-free (amino acid) in Dextrose Injection				
NDA # 19-520				
Drug Product Travasol-sulfite-free (amino acid) in Dextrose w/ Electrolytes Inj.				
NDA # 20-147				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
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	X
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion: Literature reports				
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:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
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.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				

Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1				
Investigation #2				
Investigation #3				
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	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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:				

/S/ 4-07-00

Signature of PM/CSO Date:

/S/ 4-11-00

Signature of Division or Office Director Date:

cc:
Original NDA
HFD-510/Division File
HFD-93/Mary Ann Holovac
HFD-104/TCrescenzi

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

PATENT CERTIFICATION

Baxter Healthcare Corporation certifies that, to the best of its knowledge, there are no active, competitor patents that claim the drug substance, drug product or method of using the drug product that would affect the marketability of the proposed product.

DLehmyer for Marcia Marcia — March 31, 2000

Marcia Marconi, Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20678	**Trade Name:**	CLINIMIX E + DXT IN CLAR. DUAL CHAMBER
Supplement Number:	3	**Generic Name:**	AMINO ACID+ELECTROLYTES +DEXTROSE+CALCIU
Supplement Type:	SE8	**Dosage Form:**	Injectable; Injection
Regulatory Action:		**Proposed Indication:**	

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

X NeoNates (0-30 Days) X Children (25 months-12 Years)
X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy	
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Labeling supplement containing information (clinical data by reference) on pediatric use in response to the Final Rule published in the Code of the Federal Register dated December 13, 1994. The Sponsor has revised the WARNINGS, PRECAUTIONS, and the DOSAGE AND ADMINISTRATION sections of the package insert. The revised labeling dated March 28, 2000 is acceptable and should be approved. April 4, 2000.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN MCCORT

/S/ 3-04-2000

Signature Date

MEMORANDUM

April 3, 2000

RE: Financial Disclosure Statement for Pediatric Labeling Supplements

NDAs: 19-520/s-018, 20-147/s-006, 20-678/s-003, and 20-734/s-003

DATE SUBMITTED: 03/31/2000

DATE REVIEWED: 04/03/2000

SPONSOR: Baxter

In their financial disclosure statement, Baxter asserts that, "the studies submitted in support of the pediatric labeling statements do not meet the definition of "covered clinical study."

The language that has been added to the labels of the above sNDSs in response to the final rule for pediatric labeling does not constitute information directly related to efficacy, nor does the language related to safety come from a single investigator.

Comment

The submitted supplemental NDAs listed above may be considered exempt from the regulations regarding financial disclosure.

/S/

Eric Colman, MD

cc: NDA files

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 4

FINANCIAL DISCLOSURE

Under the Guidance Financial Disclosure by Clinical Investigators issued October 25, 1999, the studies submitted in support of the pediatric labeling statements do not meet the definition of "covered clinical study." The definition of "covered clinical study" includes a requirement that the study in question be one that the "applicant or FDA relies on to establish that the product is effective." After reviewing all the studies obtained in a literature search and submitted in support of the pediatric labeling statements, Baxter concluded that the studies were not adequate and well-controlled to establish efficacy in the pediatric population. The actual pediatric use statement, as modified by FDA is:

> *Safety and effectiveness of (name of drug) in pediatric patients have not been established by adequate and well-controlled studies. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is referenced in the medical literature."*

The studies were used as the basis for adding warnings or precautions to the labeling but were not used to establish efficacy of the drug in pediatric patients.

Since the studies in question do not fall under the definition of covered studies, the Financial Disclosure regulations do not require disclosure of financial arrangements or certification of the absence of financial arrangements.

APPEARS THIS WAY
ON ORIGINAL

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ATTACHMENT 3

DEBARMENT CERTIFICATION

CERTIFICATION PER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

In accordance with section 306(k) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a(k)(1)), Baxter Healthcare Corporation certifies that Baxter Healthcare Corporation did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this application.

In addition, in accordance with section 306(k) of the Act (21 U.S.C. 335a(k) (2)), Baxter Healthcare Corporation certifies that there are no convictions that occurred within 5 years of today's date, for which a person can be debarred, of the applicant and affiliated persons responsible for the development or submission of the application.

for Marcia Marconi

March 31, 2000

Marcia Marconi, Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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DSI audit not needed for this application.

Safety Update review not needed.

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Statistical review not needed.

Biopharmaceutics review not needed.

Pharmacology Review not needed.

Chemistry review not needed.

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EER not needed.

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Microbiology review not needed.

Advisory committee meetings not necessary.

The Final Rule regarding pediatric labeling requirements was published in the Code of Federal Regulations on December 13, 1994, titled "Specific Requirements on Content and Format labeling for Human Prescription Drugs: Revision of Pediatric Use Subsection in the Labeling," Vol 59, No. 238, Pages 64240-64250.

Advertising Material was not submitted.

The Sponsor did not submit an an Integrated Summary of Safety. Refer to the Integrated Summary of Effectiveness for a summary of the relevant information that supports this application.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-678/S-003

JUL 22 1999

Baxter Healthcare Corporation
Route 120 and Wilson Road; RLT -10
Round Lake, IL 60073

Attention: Marica Marconi,
Vice President, Regulatory Affairs
I.V. Systems Divison

Dear Ms.Marconi:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Clinimix E™ sulfite- free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container
NDA Number:	20-678
Supplement Number:	S-003
Date of Supplement:	July 6, 1999
Date of Receipt:	July 7, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 5, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-678/S-003
HFD-510/Div. Files
HFD-510/CSO/McMort

filename: C:\WPFILES\20678ACK.FRM

SUPPLEMENT ACKNOWLEDGEMENT