CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-678/S003

MEDICAL REVIEW(S)

MEDICAL REVIEW
Of a MINOR AMENDMENT

Type of Submission: Minor Amendment to Pediatric labeling supplement
NDAs: 20-678 S-003
Product: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections
Company: Baxter Healthcare Corporation
Date of Submission: March 27, 2000
Date of Medical Review: March 29, 2000

As requested and shown below, the sponsor has provided the appropriate language for the Pediatric Use subsection under the Precautions section.

Dextrose is safe and effective for the stated indications in pediatric patients. As reported in the literature, the dosage selection and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed in pediatric patients, particularly neonates and low birth weight infants.
Safety and effectiveness of Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections 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.

Recommendation: **This supplement should be approved.**

/S/

Moshe Zilberstein, MD

Cc: NDA file

/S/ 3/31/00

APPEARS THIS WAY
ON ORIGINAL

MEDICAL REVIEW

Type of Submission: Pediatric labeling supplement
NDAs: 20-678 S-003
Product: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections
Company: Baxter Healthcare Corporation
Date of Submission: July 06, 1999
Date Received, DMEDP: July 07, 1999
Date of Medical Review: March 10, 2000

Background
The sponsor has submitted a Supplemental Application-Pediatric Labeling Statements. This is in response to the Final Rule published in the Code of the Federal Regulations on December 13, 1994 titled, Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revisions of "Pediatric use" Subsection in the labeling.
The above referenced Final Rule (21 CFR 201.57(f)(9)(iii)) states, "If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The Pediatric use subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subset of the pediatric population, differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections."

Has the Sponsor proposed a new indication for the pediatric population? No

Has the Sponsor made the claim that the product is safe and effective in the pediatric population? Yes, the company proposed the following language in the respective sections/subsections:

In the Precautions section, Pediatric Use subsection:

Dextrose is safe and effective for the stated indications in pediatric patients (see Indications and Usage). As reported in the literature, the dosage selection and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. Frequent monitoring of serum glucose concentrations is required when dextrose in prescribed in pediatric patients, particularly neonates and low birth weight infants.

Safety and effectiveness of amino acid injections 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 well established in the medical literature. See Dosage and Administration.

In the Warnings section:

In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage.

In Dosage and Administration section, Pediatric Use subsection:

Use of Clinimix® -sulfite-free ——————— *Injections in pedictric patients is governed by the same considerations that affect the use of any amino acid solution in pediatrics. The amount administered is dosed on the basis of grams of amino acids/kg of body weight/day. Two to 3 g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Solution administrated by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L).*

In Dosage and Administration section, Peripheral Vein Administrations subsection:

In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Has the Sponsor proposed dosing for the pediatric population? Yes, see above.

Recommendations:
The proposed wording under the Warnings and Dosage and Administration sections is acceptable. However, the proposed wording for the Pediatric Use Subsection is not acceptable.

The Pediatric Use subsection should include the following language:
Safety and effectiveness of Clinimix® -sulfite-free (——————— Injections 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.

Dextrose is safe and effective for the stated indications in pediatric patients. As reported in the literature, the dosage selection and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. Frequent monitoring of serum glucose concentrations is required when dextrose in prescribed in pediatric patients, particularly neonates and low birth weight infants.

/S/

Moshe Zilberstein, M.D.

cc: NDA Arch, McCort, Colman

/S/ 3/31/99

APPEARS THIS WAY
ON ORIGINAL