CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	20,800	APPLICATION TYPE:	Amendment
SPONSOR:	Hollister-Stier	PRODUCT/PROPRIETARY NAME:	Twinject
		USAN Established Name:	Epinephrine
CATEGORY OF DRUG:	adrenergic agonist	ROUTE OF ADMINISTRATION:	IM
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	24 January 2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
26 July 2002	29 July 2002	Amendment	See overview below

Overview of Application/Review: The sponsor has submitted a detailed response to Chemistry concerns included in the approvable letter to the sponsor of 18 December 2001. From a clinical standpoint, this NDA has been determined to be sufficient to allow approval since the original NDA submission in 1996. A short safety update consisting of brief comments on references in the clinical literature was also included in the current submission. The data included in this safety update does not raise any safety concerns for this drug product. The sponsor has also submitted draft labeling that has been updated. The following changes in the labeling are recommended: 1) change the first two sentences under the Precautions section to put more emphasis on the use of epinephrine in the life-threatening situation for which this drug product is intended. For example, "Twinject is not intended as a substitute for immediate medical attention or hospital care [redacted], 2) change the third sentence under the Precautions section to read, "Twinject [redacted] suitable for patients with such disabilities as severe debilitating arthritis of the hands, because the use of this product requires some manual dexterity to administer"; 3) under the Patient Information insert, d[redacted]

During the review period, these recommended changes were discussed with the sponsor, who agree to incorporate them into the labeling for this drug product.

Outstanding Issues: none

Recommended Regulatory Action: The drug product should be approved from a clinical standpoint.

N drive location:

NDAs:

Efficacy / Label Supp.: ___x___ Approvable _____ Not Approvable

Signed: Medical Reviewer: Richard Nicklas MD Date: 1/24/2003

Medical Team Leader: Eugene Sullivan MD Date: _____

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

/s/

Richard Nicklas
1/24/03 10:45:26 AM
MEDICAL OFFICER

Eugene Sullivan
1/24/03 11:27:42 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:NDA	20,800	APPLICATION TYPE:	Original NDA and response to letter
SPONSOR:	Hollister-Stier	PRODUCT/PROPRIETARY NAME:	TwinJect
		USAN Established Name:	Epinephrine
CATEGORY OF DRUG:	Adrenergic agonist	ROUTE OF ADMINISTRATION:	Injection
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	11 August 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
5 December 1996 and 21 April 2000	9 December 1996 and 24 April 2000	Original NDA and supplement	see overview below

Overview of Application/Review: This drug product is approvable based on the well-defined effectiveness of epinephrine in the treatment of life-threatening allergic reactions and asthma, the demonstration that the device will deliver the drug product as indicated, and the relative safety of administering epinephrine under life-threatening circumstances. On 17 February 2000, an approvable letter was sent to the sponsor indicating what was necessary in order to obtain approval for this product. In addition to a number of chemistry issues and some labeling changes, the sponsor was asked to "Provide a study evaluating the time necessary for patients with disabilities, such as debilitating arthritis, in performing the steps necessary for preparing the second dose of epineprhine." And told that "if a study is not conducted, the label must indicate that the product is not suitable for patients with such disabilities." In the submission of 21 April 2000, the sponsor states under the General Precautions section of the labeling that, " [redacted] is not suitable for patients with such disabilities as [redacted] arthritis, because the use of this product [redacted] some manual dexterity to administer." The sponsor has made the change in the labeling that was required by the Division. To more accurately state this, the labeling should be changed to read, [redacted] is not suitable.....because the use of this product requires some manual dexterity to administer. In addition, it is strongly recommended that the sponsor further study the time necessary for patients with disabilities to prepare the second dose of epinephrine, although we are not requesting a formal commitment by the sponsor on this issue. The labeling for this drug product requires additional extensive revisions (see detailed review below).

Outstanding Issues: Labeling changes are needed and the sponsor needs to consider performing studies to assess the functionality of the device in patients with disabilities.

Recommended Regulatory Action: Approvable with labeling changes.

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __x__ Approvable _____ Not Approvable

Signed: Medical Reviewer: LSI Date: 8/25/2000

Medical Team Leader: LSI Date: 8/25/2000

I. BACKGROUND: This drug product, TwinJect (previously [redacted] Epinephrine Injection contains [redacted] cc of epinephrine 1:1000 designed to deliver two doses of [redacted] (0.3 mg) subcutaneously or intramuscularly to patients [redacted] who develop anaphylaxis or severe asthma. Each cc of this drug product contains [redacted] of levo-epinephrine HCL, as well as sodium chloride, chlorbutanol and sodium bisulfite. Injectable epinephrine for emergency situations has been marketed by the sponsor and former subsidiary companies as an Ana-Kit. The TwinJect design was introduced in 1989. Both the Ana-Kit and the TwinJect deliver two manual doses of epinephrine.

TwinJect is an improved drug delivery system consisting of an automatic needle insertion/injection device and an existing marketed and approved drug/syringe product, [redacted] Epinephrine Injection USP 1:1000. The first dose of epinephrine is delivered automatically, after the patient prepares the TwinJect for firing and the second dose, if needed, manually, after partial disassembly.

II. CLINICAL: As clinical support for this NDA, the sponsor has submitted 45 articles from the clinical literature dealing with the pharmacodynamics, pharmacokinetics, toxicology and clinical efficacy of epinephrine in the treatment of anaphylaxis and asthma. There is also a brief review of these articles and the role of epinephrine in the treatment of these conditions. In the pre-NDA meeting with the sponsor of 1 March 1996, it was indicated that submission of such studies would be acceptable as confirmation of the efficacy and safety of the administration of epinephrine by injection in the treatment of anaphylaxis and severe asthma.

III. LABELING:

A. DESCRIPTION SECTION: In line 3, the third sentence should state that the second manually administered dose is also 0.3 mL., i.e. "A second 0.3 mL dose, [redacted] ....". In addition, the sponsor should provide an appropriate discussion on how the labeling should be worded to provide information to the health care provider about discarding the product after use. For example, [redacted] mL will be left after two administrations of 0.3 mL. What should the patient do with the remaining epinephrine? Is there a situation where it would be appropriate to use the remaining amount of epinephrine? etc.

B. CLINICAL PHARMACOLOGY SECTION: The labeling states that, "

Epinephrine also relaxes smooth muscle in the non-pregnant uterus. Therefore, the word " **" should be removed from the seventh sentence in this section.**

The labeling states that, " **." This would be better stated, "**

C. INDICATIONS AND USAGE SECTION:

1. The first sentence should be changed to read, "

2. **should be changed to read, "Anaphylaxis** **to stinging insects (** **Hymenoptera, which includes bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g. triatoma, mosquitos)."**

3. **should be changed to read, "**

4. **should be changed to read, "**

5. The sentence which follows after the three listed indications should be changed to read, " **may occur within minutes of** **exposure**

6. The sentence in the next to last paragraph should be changed to read,

7. The last sentence in this section should be changed to read, "

D. <u>CONTRAINDICATIONS SECTION</u>:

1. Replace the which now comprises the with the following

2. The in the should be replaced with the following statement, "

3. The sponsor should either provide us with a reference for the data which supports the statement in the [redacted], i.e. "[redacted] or the statement should be deleted. In addition, if the data does support this statement, some form of treatment is necessary for such patients and should be indicated in an additional sentence, e.g. "[redacted]

4. The one sentence in the [redacted] which reads, "[redacted] should be deleted. In the situation for which it is proposed, this drug product should be administered even if the patient is receiving other sympathomimetic agents.

5. Additional [redacted] should be added to this section, which state, [redacted]

E. <u>WARNINGS SECTION</u>:

1. The [redacted] sentence in the second paragraph should be deleted. It is unnecessary and misleading under the circumstances for which the use of this drug product is proposed.

2. The third paragraph should be changed to read, "Epinephrine is the preferred treatment for [redacted] or other emergency situations, even though this product contains sodium bisulfite, a sulfite that may in other products cause allergic-type reactions, [redacted] The alternatives to using epinephrine in a life-threatening situation [redacted]. The presence of sulfites in this product should not deter administration of the drug for treatment of [redacted] allergic or other [redacted] emergency situation."

3. The fourth paragraph should be changed to read, "Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease, and hypertension. In patients with coronary insufficiency or ischemic heart disease , epinephrine may precipitate or aggravate angina pectoris, as well as produce [redacted] ventricular arrhythmias. [redacted] [redacted] It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute life-threatening situation. [redacted]

4. An additional paragraph should be added to read, "Epinephrine is light sensitive and should be stored in the [redacted] provided. Store at room temperature. Do not refrigerate. [redacted] If the solution is discolored or contains a precipitate, replace [redacted] TwinJect."

F. GENERAL PRECAUTIONS SECTION:

1. The first sentence should be changed to read, "In conjunction with the administration of Epinephrine [redacted] the patient should seek appropriate medical attention [redacted]

2. The third sentence should be changed to read, "

3. The fourth sentence should be changed to read, '

4. Remove " from the beginning of the fifth sentence.

G. INFORMATION FOR PATIENTS SECTION: The second paragraph in this section should be changed to read, "Epinephrine may produce symptoms include an increase in pulse rate, the sensation of a more forceful heartbeat, palpitations, a throbbing headache, pallor, a feeling of overstimulation, anxiety, weakness, shakiness, dizziness or nausea. These symptoms usually subside rapidly, especially with rest, quiet, and recumbency. Patients with hypertension or hyperthyroidism could develop more severe or persistent effects and patients with coronary artery disease could experience angina. Patients with diabetes may following epinephrine administration. Patients with Parkinson's disease may notice a temporary worsening of symptoms."

H. DRUG INTERACTIONS:

1. The first sentence (first paragraph) should be changed to read, "Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

2. The in the second paragraph should be deleted.

3. The n the third paragraph should be deleted.

I. CARCINOGENSIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY SECTION: No changes in this section are needed.

J. PREGNANCY SECTION:

1. The sentence should be changed to read, "Although there are no adequate or well-controlled studies in pregnant women, epinephrine crosses the placenta.

2. The last sentence should be changed to read, "Epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus."

K. ADVERSE REACTIONS SECTION: The following sentence should be added to this section, " The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in

L. OVERDOSAGE SECTION: This section is acceptable as currently written.

M. DOSAGE AND ADMINISTRATION SECTION:

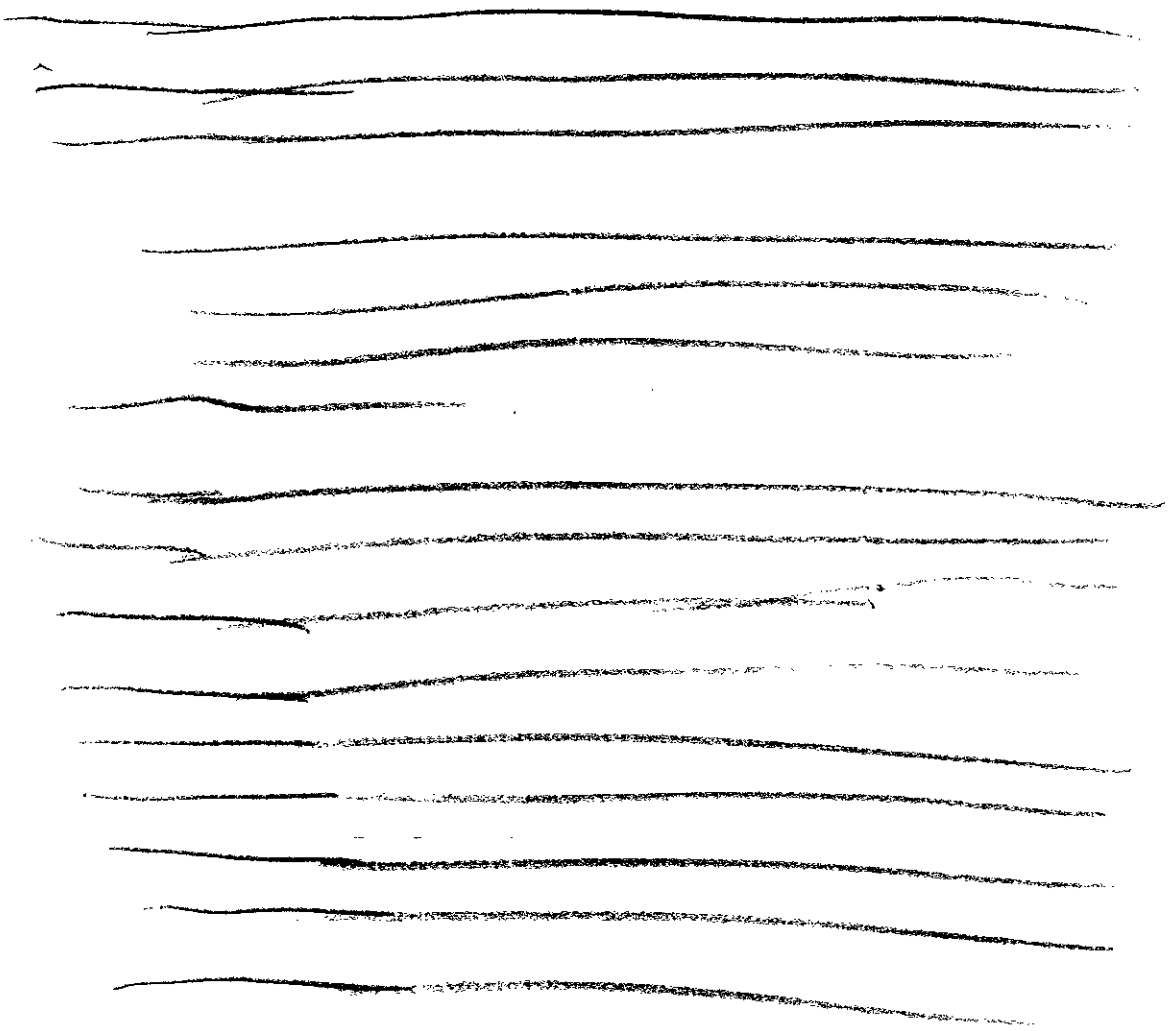
1. The sentence of the paragraph should be changed to read, "Patients should If develops a pinkish color or becomes darker than slightly yellow , the patient should physician for a replacement , since these changes indicate that the effectiveness of the drug product may be decreased.

2. The second sentence in the fourth paragraph should be changed to read,

3. The should be changed to read,

4. The following sentences should be added to this section:

N. HOW SUPPLIED SECTION: The first paragraph should be changed to read, "The TwinJect is a patient-actuated device which contains 1 mL of Epinephrine Injection USP (1:1000), of which an initial 0.3 mL can be delivered by autoinjection and a second dose of 0.3 mL is available manual administration. The is left after these two should be discarded with the device."



IV. ISSUE FOR CONSIDERATION: The sponsor was asked at the meeting of 1 March 1996 to include in their performance appraisal of this drug product: 1) the time necessary for the patient, including individuals with disabilities such as rheumatoid arthritis, to perform the procedures necessary for the administration of the second manually injected dose of epinephrine; and 2) the ability of the device to deliver the drug product through various types of clothing. The sponsor has performed the latter testing but not the former. The sponsor should be requested to study the ability of patients with disabilities to perform the procedures necessary for the administration of the second manually injected dose of epinephrine.

V. CONCLUSIONS: This drug product is appovable based on the well-defined effectiveness of epinephrine in the treatment of life-threatening allergic reactions and asthma, the demonstration that the device will deliver the drug product as indicated, and the relative safety of administering epinephrine under life-threatening circumstances. The labeling for this drug product, however, requires extensive modifications.

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:NDA	20,800	APPLICATION TYPE:	Original NDA submission
SPONSOR:	Hollister-Stier	PRODUCT/PROPRIETARY NAME:	TwinJect
		USAN Established Name:	Epinephrine
CATEGORY OF DRUG:	Adrenergic agonist	ROUTE OF ADMINISTRATION:	SQ/IM
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	8 February 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
5 December 1996	9 December 1996	Original NDA	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
None	None	None

Overview of Application/Review: This drug product is approvable based on the well-defined effectiveness of epinephrine in the treatment of life-threatening allergic reactions and asthma, the demonstration that the device will deliver the drug product as indicated, and the relative safety of administering epinephrine under life-threatening circumstances. The labeling for this drug product, however, requires extensive revisions. In addition, the sponsor needs to evaluate the time necessary for patients with disabilities to perform the procedures necessary for the administration of the second manually injected dose of epinephrine.

Outstanding Issues: Labeling changes are needed and the sponsor needs to agree to perform studies to assess the functionality of the device in patients with disabilities.

Recommended Regulatory Action: Approvable with labeling changes

N drive location: n:\ana2

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __x__ Approvable _____ Not Approvable

Signed: Medical Reviewer: LSI Date: 2/11/2000

Medical Team Leader: LSI Date: 2/11/2000