# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-800**

# PHARMACOLOGY REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Chemistry Consult #2

NDA 20800

Reviewer: C. Joseph Sun, Ph. D.
Submission date: April 21, 2000
Date of consult request: July 25, 2000
Review completed: Aug. 2, 2000
Information to be conveyed to sponsor: Yes ( ), No ( x )
Sponsor: Holliter-Stier Laboratories
Drug name: — (TwinJect) Epinephrine Injection (1:1000)
Proposed maximum recommended dose: two subcutaneous or intramuscular injections of 0.3 ml (0.6 mg in total)

Review:

Dr. Chong-Ho Kim, the review chemist, requested a safety evaluation of the applicant's proposed shelf-life ( — limit of NMT — for the —

The estimated maximum intake of — based on the proposed limit and recommended dose would be — per episode or — based on 50 kg of body weight.

Although — has been reported to cause severe allergic reactions after a single intravenous injection of products marketed in syringes with — containing — adverse reactions are usually less rapid and severe when allergens are administered intramuscularly or subcutaneously. It has been recommended that intravenous administration should not continue to occur (See memo of March 19, 1990 by Dr. Judi Weissinger, HFD-502).

The toxicity of — has been extensively studied. It was negative in the Ames test —, in vivo micronucleus test in mice ( — and HGPRT mutation assay in Chinese hamster ovary cells —. However, it has been found to be genotoxic as it increased the frequency of chromosomal aberrations and sister chromatid changes in Chinese hamster ovary cells — and showed a positive response in a mouse L5178Y lymphoma assay ( —. In NTP studies —, it has been shown to have some evidence of carcinogencicity (leukemia, pancreas, pituitary gland and adrenal gland tumors) in rats at oral doses of 375 and 750 mg/kg/day and equivocal evidence of hepatic tumors in female mice at 750 mg/kg/day.

Based on the incidence of the two major tumor findings (pituitary gland: control ,15/49; low dose, 24/50; high dose, 25/50 and adrenal gland: control, 18/50; low dose, 27/50; high dose 24/49) in the rat study and an acceptable cancer risk of $1 \times 10^{-6}$, the estimated safe human daily oral intake would be [redacted] Excellent oral absorption of [redacted] was demonstrated in rats in that 60-100% of the orally administered dose appeared in the urine. The acceptable human daily sc or im dose would therefore be no less than [redacted] assuming an oral bioavailability of 0.6 or better, and this acceptable level provides some margin of safety for the intended single im or sc dose of [redacted] of the product. Thus, the carcinogenic potential is not of concern when considered in the context of the [redacted] level and limited use.

Recommendation:

The proposed shelf-life [redacted] limit of NMT [redacted] for [redacted] of this product is acceptable

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C. Joseph Sun, Ph.D.

Orig NDA
HFD-570/Sun/Huff/Kim/Jafari

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | | | **REQUEST FOR CONSULTATION** | |
|---|---|---|---|---|
| TO (*Division Office*): *Dr. Joe Sun / Pharm/Tox Team Leader*<br>*DPADP , HFD-570* | | | FROM: Chong-Ho Kim, Ph.D., HFD-570 | |
| DATE<br>July 25, 2000 | IND NO. | NDA NO.<br>20-800 | TYPE OF DOCUMENT<br>amendment | DATE OF DOCUMENT<br>April 21, 2000 |
| NAME OF DRUG<br>TwinJect | | PRIORITY CONSIDERATION<br>3 | CLASSIFICATION OF DRUG<br>S | DESIRED COMPLETION DATE<br>ASAP |

NAME OF FIRM: Hollister-Stier Laboratories LLC

**REASON FOR REQUEST**

**1. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY_____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☒ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER (*Specify below*)

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER | ☐ CHEMISTRY<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN - VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNISES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (*List below*)
- ☐ COMPARATIVE RISK ASSASSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKET EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*) :

See "attachment".

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (*Check one*)<br>☐ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

1S1

**FORM FDA 3291 (7/83)**

cc: **NDA 20-800 File**
**HFD-570/Division File**
*HFD-570/CHKim*
*HFD-570/LJafari*

HFD-570, Division of Pulmonary and Allergy Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Labeling Review

NDA: 20800

Type of submission: Orig Amendment
Date of submission: Nov. 10, 1997
Reviewer: C. Joseph Sun, Ph. D.
Review Completed: Feb. 8, 2000

Sponsor: Hollister-Stier Lab.

Drug Name: — [Epinephrine USP (1:1000) Injection]

Review:

Original pregnancy category C section reads: "Epinephrine has been shown to

The applicant responded to Dr. Shannon Williams' request of providing preclinical information regarding teratology studies cited in the labeling.

The applicant provided three articles from the literature that may support a more meaningful statement regarding the teratogenic effects (pregnancy C category) of epinephrine in the labeling.

Rabbits given subcutaneous doses of 1.2 mg/kg (14.4 $mg/m^2$) on days 3 to 5, 6 to 7 or 7 to 9 days of gestation period exhibited arrested fetuses, decreased implantation sites and gastroschisis (J. Reprod. Fert. 27:281-282,1971).

In a teratology study, mice were given subcutaneous dose of 0.1 to 10 mg/kg on days 6-15 of the gestation period. Epinephrine produced delays in skeletal ossification at doses of 1 mg/kg (3 $mg/m^2$) and above. No such effects were reported at doses of 0.5 mg/kg (1.5 $mg/m^2$) and below (Fundamentals in Applied Toxicology 17:696-722,1991).

In hamsters, subcutaneous doses of 0.5 mg/kg (4 $mg/m^2$) given on days 7-10 of the gestation period caused preimplantation loss and delays in ossification (Teratology 23:287-291,1981).

Based on the maximum recommended daily sc or im human dose of 0.6 mg (0.012 mg/kg or 0.44 $mg/m^2$ based on 50 kg and Km factor of 37 for humans), the pregancy category C section of the labeling should be revised as follow:

"Epinephrine has been shown to have developmental effects in rabbits at a subcutaneous dose of 1.2 mg/kg (approximately 33 times the maximum recommended daily subcutaneous or intramuscular dose on a $mg/m^2$ basis), in mice at a subcutaneous dose of 1 mg/kg (approximately 7 times the maximum recommended daily subcutaneous or intramuscular dose on a $mg/m^2$ basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg (approximately 9 times the maximum recommended daily subcutaneous or intramuscular dose on a $mg/m^2$ basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a $mg/m^2$ basis)."

Recommendation:

The above-mentioned version of the pregancy category C section of the labeling should be conveyed to the applicant.

/S/

C. Joseph Sun, Ph. D.

Orig.NDA
HFD-570/Division file
HFD-570/Sun/Huff/Jafari

/S/

Division of Pulmonary And Allergy Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Chemistry Consult

NDA: 20800
Date of Consult Request: January 11, 2000
Type and Date of Submission: Amendment, Aug.16, 1999
Reviewer: C. Joseph Sun, Ph. D.
Review Completed: Feb.9, 2000
Information to be conveyed to Sponsor: No
Sponsor: Hollister-Stier Lab.

Drug Name: [redacted] [epinephrine (1:1000) Injection]

Proposed maximum recommended dose: two subcutaneous or intramuscular injections of 0.3 ml (0.6 mg)

Review:

Dr. Chong-Ho Kim, the review chemist, requested a safety evaluation of the applicant response to the item 1.d in our deficiency letter of Nov. 8, 1998. The item is "Chemical characterization as well as pharmacological/toxicological information on the [redacted] should be provided."

Hollister-Stier stated (1) that with respect to chemical characterization of [redacted] has shown them to be [redacted] and they are not related to epinephrine and (2) that the total [redacted] content of the [redacted] used in this product complies with USP Chapter< 88 >Biological Reactivity Test/In-Vivo.

[redacted] functions as an [redacted] and as pointed out by the applicant, [redacted] have been identified as related to [redacted] Some speculative by-products of [redacted] are [redacted] and [redacted] Their structures and that of [redacted] are shown on the next page.

Chemical structure of _____ showing the _____ (within box)

Some possible by-products of _____

The applicant provided three references regarding the toxicological properties of [redacted] and mentioned that no references could be found to the toxicological properties of potential by-products of [redacted]

The maximum human intake of the extractables would be [redacted] based on the quantity of these [redacted] of less than [redacted] of preparation and the injection volume of [redacted] per episode.

Since the structures of the possible [redacted] are very similar to that of [redacted], the safety evaluation of [redacted] could be reasonably based upon the toxicity and safety information for [redacted] The following information for [redacted] is available from the Integrated Risk Information System (IRIS):

WHO acceptable oral daily intake: [redacted]
State of Maine drinking water guidelines: [redacted]
EPA oral reference dose: [redacted]
NIOSH recommended exposure limits: [redacted]
OSHA permissible exposure limits: [redacted]
Neurotoxicity (two year feeding study) and reduced implants (reproductive studies) were revealed in rats.

Furthermore, LD50s from the Registry of Toxic Effects of Chemical Substance data base in rats were [redacted] and [redacted] and in mice were [redacted] and [redacted] The limited lethality data indicates that toxicity of [redacted] by the subcutaneous route may not be significantly different than by the oral route. Thus, the safety of the small quantity of very infrequent intake of these [redacted] per episode) by subcutaneous or intramuscular route could be assessed on the permissible oral intakes of [redacted] for humans. The permissible daily oral intake of [redacted] from the IRIS is at level of [redacted] which would provide a 3-83 fold safety margin for the extractables present at the proposed level.

Recommendation:

Presence of the [redacted] in the chromatogram) at the proposed level would not impose any safety concern.

LST

C. Joseph Sun, Ph. D.

Orig. NDA
HFD-570/Division file
HFD-570/Sun/Huff/Kim/Jafari

LST

DEC 4, 1997

**DIVISION OF PULMONARY DRUG PRODUCTS**
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**
(Addendum to Original Pharmacology Review Dated October 15, 1997)

**NDA No.** 20-800

**Reviewer:** Shannon P. Williams, Ph.D.

**Addendum Date:** December 1, 1997

**Information to be Conveyed to Sponsor:** Yes ( ), No (T)

**Sponsor:** Bayer Pharmaceutical Division

**Drug Name:** — Epinephrine Injection, USP (1:1000)

The following corrections should be made to the Review and Evaluation section of the Original Pharmacology Review, dated October 15, 1997:

Page 2, paragraph one;

"Currently the Sponsor has submitted an original new drug application for — Epinephrine Injection USP (1:1000), a drug delivery system consisting of an automatic needle insertion/injection device and ~~an existing marketed and approved~~ drug/syringe product, — Epinephrine Injection, USP (1:1000).

"Currently the Sponsor has submitted an original new drug application for — Epinephrine Injection USP (1:1000), a drug delivery system consisting of an automatic needle insertion/injection device and **a currently marketed but unapproved** drug/syringe product, — Epinephrine Injection, USP (1:1000).

Page 4, paragraph one;

"The drug product, ANA-KIT® (0.3 mL USP, 1:1000) is currently marketed without an approved NDA by ~~the Sponsor~~ for all the indications sought currently.

"The drug product, ANA-KIT® (0.3 mL USP, 1:1000) is currently marketed without an approved NDA by **Wyeth-Ayerst** for all the indications sought currently.

Page 4, paragraph four;

"In conclusion, epinephrine is currently marketed without an approved NDA by ~~the Sponsor~~ for all the indications sought currently and there is extensive clinical experience with epinephrine as a safe and effective treatment for allergic reactions."

"In conclusion, epinephrine is currently marketed without an approved NDA by Wyeth-Ayerst for all the indications sought currently and there is extensive clinical experience with epinephrine as a safe and effective treatment for allergic reactions."

Shannon P. Williams, Ph.D.

cc:

Original NDA 20-800
HFD-570/Division File
HFD-570/Williams
HFD-570/Sun
HFD-570/Toyer
HFD-570/Nicklas
~~HFD-570/Himmel~~
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OCT 15 1997

**DIVISION OF PULMONARY DRUG PRODUCTS**
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**
Original NDA Review

**NDA No.** 20-800

**Submission Date:** 14 FEB 96

**Reviewer:** Shannon P. Williams, Ph.D.

**Review Completed:** October 15, 1997

**Information to be Conveyed to Sponsor:** Yes (✓), No ( )

**Sponsor:** Bayer Pharmaceutical Division

**Drug Name(s):** *Proprietary:* — Epinephrine Injection, USP (1:1000)
*Generic:* Epinephrine Auto-injector
**Class:** .....Adrenergic Agonist
**Indication:**.....Emergency treatment of allergen-induced anaphylaxis and bronchospasm
**Formulation:**..... — a patient actuated single dose auto-injection device contains a — ml Epinephrine injection , USP, (1:1000); Each ml of Epinephrine Injection, USP, (1:1000) contains 1 mg of epinephrine as the hydrochloride. — of sodium chloride, not more than — mg of chlorobutanol — ) and — of sodium bisulfite sealed under nitrogen.

**Route:** .....Subcutaneous or Intramuscular injection

**Recommended Doses:**
*Adults and Children*— . Once fired, the — auto-injection device will administer one 0.3 ml dose . A second 0.3 ml dose of epinephrine is available by manual administration. Each 0.3 ml injection contains 0.3 mg of epinephrine, with a maximum of 2 doses available = 0.6 mg Epinephrine/50 kg = 0.012 mg/kg × 37 kg/m² = 0.444 mg/m².

**Related NDAs, INDs and DMFs:**
NDA 19-430 AP 22DEC87 EPIPEN + Survival Tech. Injectable; Injection
DMF No
DMF No.

**Proposed Marketing Indications:**

**Preclinical Studies submitted with this application:** None

## REVIEW AND EVALUATION

Currently the Sponsor has submitted an original new drug application for — Epinephrine Injection USP (1:1000), a drug delivery system consisting of an automatic needle insertion/injection device and an existing marketed and approved drug/syringe product — — Epinephrine Injection, USP (1:1000).

The each unit dose ( ) of the proposed clinical formulation contains — of epinephrine as the hydrochloride, — of sodium chloride, not more than — of chlorobutanol — — and — ) of sodium bisulfite sealed under nitrogen. The levels of all excipients in the proposed clinical formulation occur at levels within the range of other currently marketed injectable drug products. Thus, there are no nonclinical concerns regarding the proposed formulation.

There were no nonclincial studies submitted in support of the current application. However, there is extensive clinical experience with epinephrine as a safe and effective treatment for allergic reactions which obviates the need for additional nonclinical studies. Known pharmacological and adverse effects of epinephrine have been summarized in a Chapter by Hoffman B.B. and Lefkowitz R.J.[1] The succeeding summary of these effects is drawn largely from information provided in the aforementioned chapter.

Epinephrine (adrenaline; Adrenalin) is an endogenous sympathomimetic catecholamine which acts as a potent stimulant at both at alpha ($\alpha_1$ and $\alpha_2$) and beta ($\beta_1$ , $\beta_2$ and $\beta_3$) adrenergic receptors. Thus, its effects on target organs are often complex and vary according to the density and or proportion of $\alpha$-and $\beta$- adrenergic receptors present.

In general, most of the actions of epinephrine can be classified into seven broad types: 1)

[1] Hoffman B.B. and Lefkowitz R.J., Catecholamines, Sympathometic Drugs and Arrenergic Receptor Antagonists. In Goodman and Gilman's The Pharmacological Basis of Therapeutics 9/e (Eds.Hardman, J.G., Limbird L.E. , Molinoff, P.B., Ruddon, R.W., and Gilman, A.E.) McGraw-Hill, 1996 pp.199-248.

peripheral excitatory action on certain types of smooth muscle, especially the precapillary resistance vessels of the skin, mucosa, and kidney and the veins where infusion of pharmacologically active concentrations produce vasoconstriction, 2) a peripheral inhibitory action (relaxation) on other types of smooth muscle such as the those in wall of the gut, in the bronchial tree and in the blood vessels supplying the skeletal muscle; 3) a cardiac excitatory action (positive inotropic and chronotropic activity due to activation of cardiac $\beta_1$ and $\beta_2$ receptors); 4) metabolic actions (increased glycolosis in the liver and muscle, and liberation of free fatty acids from adipose tissue); 5) endocrine actions (modulation of the secretion of insulin, renin, and pituitary hormones); 6) CNS actions (respiratory stimulation and subjective increased wakefulness or other subjective feelings); and 7) presynaptic actions resulting in inhibition or facilitation of the release of neurotransmitters such as norepinephrine and acetylcholine.

Epinephrine is rapidly conjugated and oxidized in the gastrointestinal mucosa and liver and thus does not reach pharmacologically active concentrations following oral administration. Absorption is slow following subcutaneous injection due to local vasoconstrictive effects but is more rapid following intramuscular injection. Although epinephrine is relatively stable in the circulating blood, it is rapidly metabolized in the liver which is rich in both Catehol-O-methyltransferase (COMT) and monamine oxidase (MAO). Epinephrine can be oxidatively deaminated to 3,4-dihydroxyphenylglycoaldehyde (DOPGAL) and then either reduced to 3,4-dihydroxyphenylethyleneglycol (DOPEG) or oxidized to 3,4-dihydroxymandelic acid (DOMA). Alternatively, epinephrine can be initially methylated by COMT to form metanephrine. The majority of metabolic products from either reaction are then metabolized by the other enzyme to form the major excretory product, 3-methoxy-4-hydroxymandelic acid (frequently called vanillymandelic acid"VMA"). Small amounts of metanephrine may also be conjugated to the corresponding sulfate or glucuronides and small portions of the aldehyde oxidation products are reduced to 3-methoxy-4-hydroxyphenylglycol.

Adverse effects of epinephrine include: disturbing fear reactions, throbbing headache, tremor, weakness, dizziness, pallor, respiratory difficulty, and palpitation. Hyperthyroid and hypertensive individuals are particularly susceptible to the untoward and pressor responses to epinephrine.

More serious adverse effects including cerebral hemorrhage and cardiac arrhythmias have also been reported following administration of epinephrine. Administration of large doses or rapid iv injection may precipitate cerebral hemorrhage due to the sharp rise in blood pressure. However, subarachnoid hemorrhage and hemiplegia have even been reported after injection of a sc. dose of 0.5 ml of the 1:1000 solution. Ventricular arrhythmias may result from the cardiac stimulatory effects of epinephrine, whereas fibrillation is more likely to occur if the drug is used during anesthesia with halogenated hydrocarbon anesthetics or in patients with organic heart disease.

Epinephrine is contraindicated in patients which are receiving non-selective β-adrenergic receptor blockers due to its unopposed action on $\alpha_1$-adrenergic receptors which may lead to severe hypertension and cerebral hemorrhage. Finally, large or repeated doses of epinephrine given to experimental animals lead to damage to arterial walls of the myocardium, which is so

severe as to cause the appearance of necrotic areas in the heart indistinguishable from myocardial infarcts.

Epinephrine is the drug of choice for providing rapid relief of serious acute hypersensitivity reactions to drugs and other allergens, (e.g. food or bee stings). The Drug product, ANA-KIT ® (0.3 ml of Epinephrine USP, 1:1000) is currently marketed without an approved NDA by the Sponsor for all the indications sought currently. In addition, the approved drug product EPIPEN (0.3 ml of Epinephrine USP, 1:1000; NDA 19-430, approved December 22, 1987) is also currently marketed in the U.S.A. In view of the extensive clinical experience with epinephrine as a safe and effective treatment for allergic reactions no additional nonclinical studies are required to support the current application.

There are no data from either animal or human studies regarding the carcinogenic or mutagenic potential of epinephrine and no studies have been conducted to determine its potential to impair fertility. However, considering the acute nature of dosing for the proposed indication, and the fact that epinephrine is an endogenous catecholamine for which there exists a vast amount of knowledge and clinical experience, no additional nonclinical studies will be required to support the current application.

**Labeling:** The proposed labeling is acceptable from a preclinical standpoint with the exception of the pregnancy section, where available references were inadequate for review. In a communication on September 26, 1997, additional references pertaining to the pregnancy section were requested from the Sponsor. Thus, review of the pregnancy section of the labeling will be deferred until the appropriate references are submitted as requested.

In conclusion, epinephrine is currently marketed without an approved NDA by the Sponsor for all the indications sought currently and there is extensive clinical experience with epinephrine as a safe and effective treatment for allergic reactions. Thus, from a nonclinical standpoint the NDA is approvable. However, the Sponsor should submit appropriate documentation which support the proposed labeling. The additional documentation needed for the labeling was requested from the Sponsor via a telecommunication on September 26, 1997.

**RECOMMENDATION**

The submitted application is approvable contingent on submission of appropriate documentation which support the proposed labeling as was requested from the Sponsor via a telecommunication on September 26, 1997.

/S/

Shannon Willimams, Ph.D.,
Pharmacologist

Original NDA 20-800
c.c. HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/TD.Toyer
HFD-570/R.Nicklas
HFD-570/S. Williams
HFD-570/M. Himmel

/S/

## LETTER TO SPONSOR

The Sponsor should be asked to submit appropriate documentation which support the pregnancy section of the proposed labeling as was requested via a telecommunication on September 26, 1997.

APPEARS THIS WAY
ON ORIGINAL