CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 18986

Trade Name: PRALIDOXIME CHLORIDE FOR AUTOINJECTION

Generic Name: PRALIDOXIME CHLORIDE FOR AUTOINJECTION

Sponsor: SURVIVAL TECHNOLOGY, INC

Approval Date: 04/26/83

Indication(s): TREATMENT OF POISONING BY NERVE AGENTS HAVING ANTICHOLINESTERASE ACTIVITY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 18986

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 18986

APPROVAL LETTER

NDA 18-986

Survival Technology, Inc.
Attention: Mr. Cabot R. Caskie
7801 Woodmont Avenue
Bethesda, MD 20814

APR 26 1983

Gentlemen:

Please refer to your new drug application dated March 28, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Pralidoxime Chloride for Autoinjection.

We also acknowledge receipt of your additional communication dated April 25, 1983.

The application was filed on April 25, 1983.

We have completed our review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/S/ 4/26/83

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

APPEARS THIS WAY
ON ORIGINAL

Enclosures: Records and Reports Requirements (Reg. 310.300)
Conditions of Approval of NDA

BLT-DO (HFR-3200)
NDA 18-986
HFN 160
HFN 616
Doc Room 160
R/D GBoyer 04/18/83 /S/ 4/26/83
R/D PHRussell 04/26/83; JPMann 04/26/83; JKinscoe 04/20/83; CPHolberg 04/25/83
FT CS 04/26/83 w0839K

APPEARS THIS WAY
ON ORIGINAL

APPROVAL

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 18-986

DATE APPROVAL LETTER ISSUED: APR 26 1983

TO: HFN-616

FROM: [XX] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [XX] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [ ] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [XX] HUMAN [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

Pralidoxime Chloride (2-PAM Chloride)

DOSAGE FORM: auto-injector

HOW DISPENSED: [XX] RX [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

pralidoxime chloride, 300mg/ml

APPEARS THIS WAY
ON ORIGINAL

NAME OF APPLICANT *(Include City and State)*

Survival Technology, Inc.
Bethesda, Maryland 20854

APPEARS THIS WAY
ON ORIGINAL

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

for use in nerve agent poisoning only

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

APPEARS THIS WAY
ON ORIGINAL

FORM PREPARED BY

NAME /S/ DATE 4/18/83

FORM APPROVED BY

NAME /S/ DATE 4/25/83

Form FD 1642 (4/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

/S/ 4/26/83

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18986

FINAL PRINTED LABELING

PRALIDOXIME CHLORIDE INJECTION (AUTO-INJECTOR)

FOR USE IN NERVE AGENT POISONING ONLY

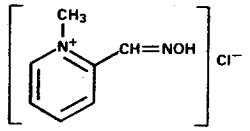
A Sterile Solution For Intramuscular Use Only

DESCRIPTION

Chemical name: 2-formyl-1-methylpyridinium chloride oxime (pyridine-2-aldoxime methochloride. Available in the United States as PROTOPAM* CHLORIDE pralidoxime chloride is frequently referred to as 2-PAM Chloride.

/S/
4-26-83

Structural formula:



Pralidoxime chloride occurs as an odorless, white, nonhygroscopic, crystalline powder which is soluble in water to the extent of 1 g in less than 1 ml. Stable in air, it melts between 215° and 225°, with decomposition.

The specific activity of the drug resides in the 2-formyl-1-methylpyridinium ion and is independent of the particular salt employed. The chloride is preferred because of physiologic compatibility, excellent water solubility at all temperatures, and high potency per gram, due to its low (173) molecular weight.

Each prefilled auto-injector provides a dose of the antidote, pralidoxime chloride, in a self-contained unit, specially designed for automatic self- or buddy-administration by military personnel. The recommended procedure (see DOSAGE AND ADMINISTRATION) is to inject the contents of the auto-injector into the muscles of an outer thigh.

When activated, each auto-injector dispenses 600 mg of pralidoxime chloride (PROTOPAM* CHLORIDE) in 2 ml of a sterile solution containing 20 mg benzyl alcohol, 11.26 mg aminoacetic acid, and Water for Injection, U.S.P. The pH is adjusted with hydrochloric acid.

After an auto-injector has been activated, the empty container should be disposed of properly (see DOSAGE AND ADMINISTRATION); it cannot be refilled nor can the protruding needle be retracted.

CLINICAL PHARMACOLOGY

Pralidoxime chloride is a cholinesterase reactivator.

The principal action of pralidoxime is to reactivate cholinesterase (mainly outside of the central nervous system) which has been inactivated by phosphorylation due to an organophosphate pesticide or related compound. The destruction of accumulated acetylcholine can then proceed and neuromuscular junctions will again function normally. Pralidoxime also slows the process of "aging" of phosphorylated cholinesterase to a non-reactivatable form, and detoxifies certain organophosphates by direct chemical reaction. The drug has its most critical effect in relieving paralysis of the muscles of respiration. Because pralidoxime is less effective in relieving depression of the respiratory center, atropine is always required concomitantly to block the effect of accumulated acetylcholine at this site. Pralidoxime relieves muscarinic signs and symptoms: salivation, bronchospasm, etc., but this action is relatively unimportant since atropine is adequate for this purpose.

Pralidoxime is distributed throughout the extracellular water; it is not bound to plasma protein. The drug is rapidly excreted in the urine partly unchanged, and partly as a metabolite produced by the liver. Consequently, pralidoxime is relatively short acting and repeated doses may be needed, especially where there is any evidence of continuing absorption of the poison.

The minimum therapeutic concentration of pralidoxime in plasma is 4 µg·ml; this level is reached in about 16 minutes after a single injection of 600 mg PROTOPAM CHLORIDE. The apparent half-life of PROTOPAM CHLORIDE is 74-77 minutes.

It has been reported[1] that the supplemental use of oxime cholinesterase reactivators (such as pralidoxime) reduces the incidence and severity of developmental defects in chick embryos exposed to such known teratogens as parathion, bidrin, carbachol and neostigmine. This protective effect of the oximes was shown to be dose related.

INDICATIONS AND USAGE

This auto-injector for pralidoxime chloride is specifically indicated for intramuscular use as an adjunct to atropine in the treatment of poisoning by nerve agents having anticholinesterase activity.

CONTRAINDICATIONS

The pralidoxime chloride auto-injector is contraindicated in patients who are hypersensitive to any component of the product.

WARNINGS

Pralidoxime is not effective in the treatment of poisoning due to phosphorus inorganic phosphates or organophosphates not having anticholinesterase activity.

PRECAUTIONS

General:

Pralidoxime has been very well tolerated in most cases, but it must be remembered that the desperate condition of the organophosphate-poisoned patient will generally mask such minor signs and symptoms as have been noted in normal subjects.

Because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug. Thus, the dosage of pralidoxime

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Because pralidoxime is excreted in the urine, a decrease in renal function will result in increased blood levels of the drug. Thus, the dosage of pralidoxime should be reduced in the presence of renal insufficiency.

Information for patients:

The pralidoxime chloride auto-injector should be self- or buddy-administered by military personnel only after the following events have occured:

- individual has donned his mask subsequent to recognizing the existence of a chemical agent hazard in his area
- some or all of the symptoms of nerve agent poisoning cited below are present:
  - unexplained runny nose
  - tightness of chest with difficulty in breathing
  - pinpointed pupils of the eye resulting in blurred vision
  - drooling, excessive sweating
  - nausea, vomiting, and abdominal cramps
  - involuntary urination and defecation
  - jerking, twitching, and staggering
  - headache, drowsiness, coma, convulsions
  - stoppage of breathing

Appropriate steps must be taken to insure that personnel equipped with auto-injectors understand their indications and use including review of symptoms of poisoning and operation of the auto-injector.

Laboratory tests:

Treatment of organophosphate poisoning should be instituted without waiting for the results of laboratory tests. Red blood cell, plasma cholinesterase, and urinary paranitrophenol measurements (in the case of parathion exposure) may be helpful in confirming the diagnosis and following the course of the illness. A reduction in red blood cell cholinesterase concentration to below 50% of normal has been seen only with organophosphate ester poisoning.

Drug interactions:

When atropine and pralidoxime are used together, the signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when atropine is used alone. This is especially true if the total dose of atropine has been large and the administration of pralidoxime has been delayed.[2,3,4]

The following precautions should be kept in mind in the treatment of anticholinesterase poisoning, although they do not bear directly on the use of pralidoxime: since barbiturates are potentiated by the anticholinesterases, they should be used cautiously in the treatment of convulsions; morphine, theophylline, aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers should be avoided in patients with organophosphate poisoning.

Carcinogenesis, mutagenesis, impairment of fertility:

Since the pralidoxime chloride auto-injector is indicated for short-term emergency use only, no investigations of its potential for carcinogenesis, mutagenesis, or impairment of fertility have been conducted by the manufacturer, or reported in the literature.

Pregnancy category C:

Animal reproduction studies have not been conducted with pralidoxime. It is also not known whether pralidoxime can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pralidoxime should be given to a pregnant woman only if clearly needed.

Nursing mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pralidoxime is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Forty to 60 minutes after intramuscular injection, mild to moderate pain may be experienced at the site of injection.

Pralidoxime may cause blurred vision, diplopia and impaired accomodation, dizziness, headache, drowsiness, nausea, tachycardia, increased systolic and diastolic blood pressure, hyperventilation, and muscular weakness when given parenterally to normal volunteers who have not been exposed to anticholinesterase poisons. In patients it is very difficult to differentiate the toxic effects produced by atropine or the organophosphate compounds from those of the drug.

Elevations in SGOT and/or SGPT enzyme levels were observed in 1 of 6 normal volunteers given 1200 mg of pralidoxime chloride intramuscularly, and in 4 of 6 volunteers given 1800 mg intramuscularly. Levels returned to normal in about 2 weeks. Transient elevations in creatine phosphokinase were observed in all normal volunteers given the drug. A single intramuscular injection of 330 mg in 1 ml in rabbits caused myonecrosis, inflammation, and hemorrhage.

When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone. This is especially true if the total dose of atropine has been large and the administration of pralidoxime has been delayed.[2,3,4] Excitement and manic behavior immediately following recovery of consciousness have been reported in several cases. However, similar behavior has occurred in cases of organophosphate poisoning that were not treated with pralidoxime.[3,5,6]

DRUG ABUSE AND DEPENDENCE

Pralidoxime chloride is not subject to abuse and possesses no known potential for dependence.

OVERDOSAGE

Manifestations of overdosage: Observed in normal subjects only: dizziness, blurred vision, diplopia, headache, impaired accomodation, nausea, slight tachycardia. In therapy it has been difficult to differentiate side effects due to the drug from those due to the effects of the poison.

Treatment of overdosage: Artificial respiration and other supportive therapy should be administered as needed.

Acute toxicity: i.v. — man TDLo: 14 mg/kg (toxic effects: CNS)
i.v. — rat LD50: 96 mg/kg
i.m. — rat LD50: 150 mg/kg
oral — mouse LD50: 4100 mg/kg
i.p. — mouse LD50: 155 mg/kg
i.v. — mouse LD50: 90 mg/kg
i.m. — mouse LD50: 180 mg/kg
i.v. — rabbit LD50: 95 mg/kg
i.m. — guinea pig LD50: 168 mg/kg

DOSAGE AND ADMINISTRATION

Exposure to nerve agents possessing anticholinesterase activity (organophosphate type)

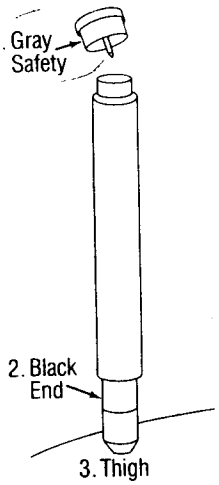
MILD CASE—headache, blurred vision, mild muscarinic signs

MODERATELY SEVERE CASE—excessive sweating, lacrimation, salivation, diarrhea, tightness in the chest

For optimal reactivation of organophosphate-inhibited cholinesterase, atropine and pralidoxime should be administered as soon as possible after exposure. Depending on the severity of symptoms, immediately administer one atropine-containing auto-injector, followed by one pralidoxime-containing auto-injector. Atropine must be given first until its effects become apparent and only then should pralidoxime be administered. If nerve agent symptoms are still present after 15 minutes, repeat injections. If symptoms still exist after an additional 15 minutes, repeat injections for a third time. If after the third set of injections, symptoms remain, do not given any more antidotes but seek medical help.

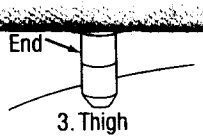
Directions for use: When, as described above, auto-injector use is indicated, proceed as follows:

1. Remove gray safety.
2. Place black end on thickest part of thigh and press hard until injector functions.
3. Hold firmly in place for ten seconds, then remove. Massage the area of injection.
4. Dispose of properly. Push ejected needle through a pocket flap (or other thick and conspicuous part of outer clothing). Bend needle into a hook.



VERY SEVERE CASE—cyanosis, respiratory embarrassment, coma
Initial measures should include removal of secretions, maintenance of a patent airway and, if necessary, artificial ventilation. Atropine should not be used *until* cyanosis has been overcome since atropine produces ventricular fibrillations in the presence of hypoxia. Morphine, theophylline, aminophyl-

through a pocket flap (or other thick and conspicuous part of outer clothing). Bend needle into a hook.



3. Thigh

VERY SEVERE CASE—cyanosis, respiratory embarrassment, coma
Initial measures should include removal of secretions, maintenance of a patent airway and, if necessary, artificial ventilation. Atropine should not be used *until* cyanosis has been overcome since atropine produces ventricular fibrillations in the presence of hypoxia. Morphine, theophylline, aminophylline, and succinylcholine are contraindicated. Tranquilizers of the reserpine or phenothiazine type are to be avoided.

"Pralidoxime is most effective if administered immediately after poisoning. Generally, little is accomplished if the drug is given more than 36 hours after termination of exposure. When the poison has been ingested, however, exposure may continue for some time due to slow absorption from the lower bowel, and fatal relapses have been reported after initial improvement. Continued administration for several days may be useful in such patients. Close supervision of the patient is indicated for at least 48 to 72 hours. If dermal exposure has occurred, clothing should be removed and the hair and skin washed thoroughly with sodium bicarbonate or alcohol as soon as possible. Diazepam may be given cautiously if convulsions are not controlled by atropine."[7]

IMPORTANT: PHYSICIANS, AND/OR OTHER MEDICAL PERSONNEL ASSISTING EVACUATED VICTIMS OF NERVE AGENTS, SHOULD AVOID EXPOSING THEMSELVES TO CONTAMINATION BY THE VICTIMS' CLOTHING.

HOW SUPPLIED

Pralidoxime chloride is supplied in aqueous solution prefilled in the auto-injector (600 mg, 2 ml) for military use. Auto-injectors are supplied through the Directorate of Medical Materiel, Defense Personnel Support Center or other analogous agency.

When activated, each auto-injector dispenses 600 mg of pralidoxime chloride [PROTOPAM® CHLORIDE] in 2 ml of a sterile solution containing 20 mg benzyl alcohol, 11.26 mg aminoacetic acid, and Water for Injection, U.S.P. The pH is adjusted with hydrochloric acid.

STORE AT ROOM TEMPERATURE (APPROXIMATELY 25° C).

KEEP FROM FREEZING

Survival Technology, Inc.
3/83 Bethesda, MD 20814 Printed in U.S.A.

REFERENCES

1. Landauer, W.: Cholinomimetic teratogens. V. The effect of oximes and related cholinesterase reactivators, Teratology *15*:33 (Feb.) 1977.
2. Møller, K.O., Jensen-Holm, J., and Lausen, H. H.: Ugeskr. Laeg. *123*: 501 1961.
3. Namba, T., Nolte, C. T., Jackrel, J., and Grob, D.: Poisoning due to organophosphate insecticides. Acute and chronic manifestations, Amer. J. Med. *50*:475 (Apr.) 1971.
4. Arena, J. M.: Poisoning. Toxicology. Symptoms. Treatments, ed. 4, Springfield, Ill., Charles C Thomas, 1979, p. 133.
5. Brachfeld, J., and Zavon, M. R.: Organic phosphate (Phosdrin®) intoxication. Report of a case and the results of treatment with 2-PAM, Arch. Environ. Health *11*:859, 1965.
6. Hayes, W. J., Jr.: Toxicology of Pesticides, Baltimore, The Williams & Wilkins Company, 1975, p. 416.
7. AMA Department of Drugs: AMA Drug Evaluations, ed. 4, Chicago, American Medical Association, 1980, p. 1455.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18986

MEDICAL REVIEW(S)

NDA 18-986

Medical Officer's Review

Date Completed: April 8, 1983

Name of Sponsor: Survival Technology, Inc.
7801 Woodmont Avenue
Bethesda, Maryland 20814

Date of Submission: March 28, 1983

Date Received: March 28, 1983

Name of Drug: Trade: Protopam

Generic: Pralidoxime chloride

Category (Use) of Drug: Cholinesterase reactivator for use in treatment of nerve gas poisoning

Dosage Form and Route of Administration: 600 mg delivered dose by automated injection device for intramuscular injection (self or buddy administered)

Type of Submission: Original NDA according to 21 CFR 314.1 and Section 505(b) of the Food, Drug and Cosmetic Act

General Comments

The submission consists of covering letter signed by Cabot R. Caskie, Excutive Vice President and consists of completed NDA application Form 356H

The only other materials provided in the application are copies of labeling as approved under NDA 18-799 with the minor exception of company name and a statement in Storage Conditions, "Keep from Freezing."

Summary and Conclusions

There is no clinical or pharmacology information presented in the application.

Recommendation

The application is medically approvable. Pending concurrence of other disciplines, letter should issue.

Approval letter could be based on agreement that FPL will be identical in content to draft labeling provided, if Chemist agrees.

/S/

Patricia H. Russell, M.D.

/S/ 4-8-83

APR 12 1983

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA 18-986
HFN-160
HFN-220
R/D PHRussell 4/8/83
R/D Init. by PHWalters for JPMann 4/8/83
Doc. Room 160

APPEARS THIS WAY
ON ORIGINAL

~~IND/NDA~~ 18-986

Medical Officer's Review

Date Completed: April 25, 1983
~~Original Approval Date~~:

Name of Sponsor: Survival Technology, Inc.
7801 Woodmont Ave.
Bethesda, Maryland 20854

Date of Submission: April 25, 1983

Date Received: April 25, 1983

APPEARS THIS WAY
ON ORIGINAL

Name of Drug: Trade: Pralidoxime Chloride Injection

~~Generic~~:

Category (Use) of Drug: Cholinesterase Reactivator

Dosage Form(s) and Route(s) of Administration: Solution of 600 mg, delivered dose, ~~for~~ in automated injection device for i.m. administration by ~~the~~ self or buddy administered dosing

APPEARS THIS WAY
ON ORIGINAL

Type of Submission: Amendment to Original NDA

The submission provides written response to questions of manufacturing controls data raised by Dr. Hoiberg in telephone conversation of 4/25/83 and includes FPL.

APPEARS THIS WAY
ON ORIGINAL

Dr. Hoiberg's request for pH and pyrogen free labeling to be included in the next printing are noted and agreed with.

APPEARS THIS WAY
ON ORIGINAL

Recommendation

The labeling is medically approvable with revision as above to me be made at the next printing.

/S/

APPEARS THIS WAY
ON ORIGINAL

Patricia H. Russell, M.D.

/S/
4/26/83

cc: NDA 18-986
HFN-160
HFN-220
Doc Rm 160

APPEARS THIS WAY
ON ORIGINAL

APR 26 1983

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18986

CHEMISTRY REVIEW(S)

Division of Surgical-Dental Drug Products
Chemist's Review #1
April 25, 1983

A. 1. NDA 18-986
Applicant: Survival Technology, Inc.
Address: 7801 Woodmont Avenue
Bethesda, Maryland
Manufacturing Site: St. Louis, Missouri

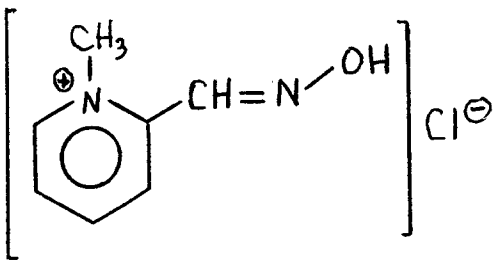
2. Product Names:
Proprietary: Pralidoxime Chloride Injection (Auto-Injector)
Non-proprietary: Pralidoxime Chloride Injection (Auto-Injector)
Code name: 2-PAM Chloride

3. Dosage Form and Route of Administration:
Dosage Form: Rx; An aqueous sterile solution (2 ml) containing 600 mg of pralidoxime chloride, 20 mg benzyl alcohol and 11.26 mg aminoacetic acid in a prefilled auto-injector.

Route of Administration: Intramuscular injection preferably into the muscles of the outer thigh.

4. Pharmacological Category and/or Principal Indication:
Antidote for nerve agent poisoning (phosphorylation of enzymes) as a cholinesterase reactivator. Accumulated acetylcholine is eliminated to permit normal function of the neuromuscular junctions. For optimal enzyme reactivation, atropine should first be injected (auto-injector) and the 2-PAM administered only after atropine yields a positive response.

5. Structural Formula and Chemical Name:
Structural Formula:



APPEARS THIS WAY
ON ORIGINAL

MW: 173

Chemical Names: See USP XX, p. 648

B. 1. Initial Submission:
Original application dated March 28, 1983, received in HFN-160 on March 28, 1983, and by supervisory chemist on April 13, 1983.

2. Amendments:
April 25, 1983

D. Conclusions and/or Recommendations:
The manufacturing and controls sections of the new drug application are acceptable from a chemistry viewpoint.

APPEARS THIS WAY
ON ORIGINAL

/S/

Charles P. Hoiberg, Ph.D.
Supervisory Chemist

NDA 18-986
HFN-160, HFN-102 (Kumkumian)
doc room 160
R/D CPHoiberg HFN-160 4/25/83
ft mw 4/25/83 w1813P

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APR 26 1983

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18986

PHARMACOLOGY REVIEW(S)

NDA 18-986

Review #1

Survival Technology, Inc.
7801 Woodmont Avenue
Bethesda, MD 20814

Date of Review: April 18, 1983

Date of Submission: March 28, 1983

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Initial Submission of March 28, 1983
Original Summary

Drug: Pralidoxime Chloride for Autoinjection

PROTOPAM^{R}
pralidoxime chloride
2-PAM Cl
2-pyridine aldoxime methochloride
2-formyl-1-methylpyridinium chloride oxime
MW 173

Formulation: 600 mg of pralidoxime chloride in 2 ml aqueous solution for im injection

	mg/ml
pralidoxime chloride	300
benzyl alcohol	20
aminoacetic acid	11.26
hydrochloric acid	
water for injection	

Category: cholinesterase reactivator

Proposed clinical indication: for intramuscular use in a self administered injector unit, as an adjunct to atropine, in the treatment of poisoning by nerve agents having anticholinesterase activity.

Comments and evaluation:

Survival Technology, Inc.

Conclusion and recommendation:

The relative safety and efficacy of the preparation have been demonstrated in preclinical studies
the application is thus recommended for approval from the standpoint of pharmacology.

Pharmacology portion of letter to Applicant:

None

APPEARS THIS WAY
ON ORIGINAL

/S/

Dou Huey Jean, Ph.D., Pharmacologist

NDA 18-986
HFN-160, HFN-220
doc room 160
HFN-102 (Glocklin)
R/D DHJean HFN-160 4/18/83
R/D Init JKInscoe 4/20/83
ft mw 4/21/83 w1803P

APPEARS THIS WAY
ON ORIGINAL

APR 22 1983

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18986

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

RECORD OF TELEPHONE CONVERSATON/MEETING

DATE: Apr 25, 1983

NDA NUMBER: NDA 18-986

IND NUMBER: NA

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Pralidoxine Chloride Injection (Auto-Injector)

FIRM NAME: Survival Technology

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Mr. Cabot R, Caskie

TELEPHONE NO.: 654-2303

Mr. Caskie was contacted to obtain the following clarifications and commitments:

1. Survival Technology will be performing all the release tests as described in NDA 18-799(Ayerst) including the stability-indicating procedure

2. The expiration period for their drug product will be 3 years

3. Survival Tech. will collect stability data on the drug product manufactured under NDA 18-986.

4. At the next printing of the package insert, the "Description" section will be revised to include the pH range and the statement "pyrogen-free".

Mr. Caskie agreed to submit a letter to this NDA file confirming the above stated information.

cc: NDA 18-986 ✓
HFN-160

APPEARS THIS WAY ON ORIGINAL

APR 26 1983

/S/ 4/26/83

SIGNATURE

Charles P. Hoiberg /S/ 4/26/83 /S/

DIVISION: HFN-160

FORM FD 2587 (7/77)

ORIGINAL IND/NDA

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 4/22/83
FROM: Sally Schwenen, HFN-322		OFFICE
TO: Dr. C. Hoiberg, HFN-160		DIVISION
SUBJECT: NDA 18-986		

SUMMARY

This will confirm our conversation of 4/22/83.

APPEARS THIS WAY
ON ORIGINAL

Survival Technology, Inc., St. Louis, MO is presently capable of manufacturing drugs in conformity with the CGMP regs.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE	DOCUMENT NUMBER
/S/	

FORM FD 2034 (6/76)

RECORD OF TELEPHONE CONVERSATON/MEETING

DATE: April 14, 1983

NDA NUMBER: 18-986

IND NUMBER:

TELECON/MEETING

INITIATED BY: [X] APPLICANT/SPONSOR [ ] FDA

MADE: [X] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME:

I accepted a call from Mr. Caskie who was calling to asceratin the status of the NDA for Protopam which they hand delivered on March 28, 1983.

FIRM NAME: Survival Technology

Based on conversation with Dr. Mann, I informed Mr. Caskie that I forsaw no problem with the application and that a letter would probably be issuing soon.

He requested that this Division contact Paul Vogel, HFO-26 to advise him that the application is approvable so that Survival Technology

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Cabot R. Caskie, Executive Vice President

I told him that it might be possible that the letter could be an approval letter based on agreement that FPL would be identical to that submitted with the application

TELEPHONE NO. ?

The middle of April is considered the deadline to be met in order to fulfill the military contracts.

cc: NDA 18-986 ✓
HFN-160

APPEARS THIS WAY ON ORIGINAL

APR [illegible] 1983

/S/
4/14/83

SIGNATURE: /S/

DIVISION: HFN-160

FORM FD 2587 (7/77)

ORIGINAL IND/NDA

NDA 18-986

APR 06 1983

Survival Technology, Inc.
Attn: Mr. Cabot R. Coskie
7801 Woodmont Avenue
Bethesda, MD 20814

APPEARS THIS WAY
ON ORIGINAL

Dear Sir:

We are pleased to acknowledge your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of drug: Pralidoxime Chloride for Autoinjection

Date of application: March 28, 1983

Date of receipt: March 28, 1983

APPEARS THIS WAY
ON ORIGINAL

Our reference number: NDA 18-986

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you, please call:

Miss. Diane Thilman
Consumer Safety Officer
301/443-3500

APPEARS THIS WAY
ON ORIGINAL

All future communications concerning this NDA should be addressed as follows:

National Center for Drugs and Biologics HFN-160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

/S/ 4/6/83

APPEARS THIS WAY
ON ORIGINAL

James P. Mann, MD
Director
Division of Surgical-Dental
Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

NDA 18-986 /S/ 4/6/83
HFN-160
R/D: MWilson HFN-160 4/4/83
Doc Room
R/D init. by: GBoyer 4/4/83, DThilman 4/4, JPMann 4/5/83
FT Margarita 4/5/83 W0216M M2

ACKNOWLEDGEMENT

/S/ 4/5/83

No microbiology review required
/S/ 4/5/83
160

NDA 18986
original

Survival Technology, Inc.

March 28, 1983

James P. Mann, M.D.
Director
Division of Surgical-Dental Drug Products
National Center for Drugs and Biologics
HFD 160 Room 18B-08
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Mann:

According to Title 21, CFR, 314.1, pursuant to section 505(b) of the Food, Drug and Cosmetic Act, Survival Technology, Inc. is herewith submitting a New Drug Application for 600 mg of 2-pyridine aldoxime methochloride (PROTOPAM® brand; pralidoxime chloride; 2-PAM Cl) in 2 ml of an aqueous solution for intramuscular injection packaged in pre-filled Auto-Injectors

This is to provide for a New Drug Application in the name Survival Technology, Inc. for the purpose of supplying 2-PAM Cl Auto-Injectors to the United States Department of Defense.

Survival Technology, Inc.

Survival Technology, Inc. will formulate the drug dosage form, manufacture the auto-injector, and perform all other designated operations in accordance with the specifications described in

20854

7801 WOODMONT AVENUE • BETHESDA, MARYLAND 20014 • TELEPHONE (301) 654-2303

Changes have been made to the immediate container label as follows:

1. The statement "Keep from Freezing" will appear under the storage conditions statement.

2. The company name will appear as:

   Survival Technology, Inc.
   Bethesda, MD 20814

APPEARS THIS WAY
ON ORIGINAL

Final printed labels and other labeling are attached for your review

We appreciate your prompt review of this application as it relates to national security. Please let me know if we can be of further assistance or provide additional information.

Sincerely,

C. R. Caskie

APPEARS THIS WAY
ON ORIGINAL

Cabot R. Caskie
Executive Vice-President

CRC/rks

APPEARS THIS WAY
ON ORIGINAL