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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**17-516**

**Trade Name: Sinequan**

**Generic Name: Doxepin HCl**

**Sponsor: Pfizer Pharmaceuticals**

**Approval Date: March 11, 1974**

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**17-516**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**APPROVAL LETTER**

AF 12-118

MAR 11 1974

NDA 17-516

Pfizer Pharmaceuticals  
Pfizer, Incorporated  
Attention: Michael A. Hospador, Ph.D.  
235 East 42nd Street  
New York, New York 10017

Gentlemen:

Reference is made to your new drug application dated July 24, 1973 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Sinequan (doxepin HCl) Oral Concentrate, 10 mg./cc.

We also acknowledge receipt of your additional communications dated September 27, 1973, October 25, 1973, November 2, 1973, and February 10, 1974.

We refer to the February 15, 1974 telephone conversation between your representative, Mr. Joseph P. Aterno, and Mr. William C. Crabbs of this Administration concerning labeling for this drug. It is understood that you will expeditiously undertake labeling revisions for all dosage forms of Sinequan; the labeling for this drug requires major revision in order to bring it into conformance with present labeling guidelines. In this regard we request that you arrange a conference with the Division of Neuropharmacological Drug Products within 3 weeks of the date of receipt of this letter to discuss such labeling revisions.

It is also understood from the discussion in person on Wednesday, January 30, 1974, between your representative, Michael A. Hospador, Ph.D. and Mrs. Rachel S. Silk, chemist, of this Administration, that your firm has agreed to revise the analytical method used for identification of the drug (identification of the cis and trans isomers), to make it suitable for regulatory as well as control purposes.

We have completed the review of this application as amended 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.

It is understood that approval of the application is conditional based on the satisfactory revision of labeling and analytical methodology.

Please submit two market packages of the drug when available.

In addition, we would appreciate your submitting in duplicate the advertising copy which you intend to use in your proposed promotional or advertising campaign. Please submit one of the copies directly to the Division of Drug Advertising with a copy of the package insert.

Sincerely yours,



J. Richard Crout, M.D.  
Director  
Bureau of Drugs

Enclosures

- cc
- NYK-DO
- OSE (HFD-100)
- DND (HFD-120)
- DOC (HFD-106)
- TAS (HFD-113)
- HFD-1
- Hobart/HFD-120
- VGlock/HFD-120
- RST/K/HFD-120
- WCC/abbs 1/14/74
- Retyped 2/20/74 mcs
- R/D init. by Scoville 2/10/74

*Handwritten notes:*  
Good 2/20/74  
R. S. Hille 2-20-74  
W. S. Hille 2/20/74  
W. S. Hille 2-20-74  
J. M. Hille 2/20/74  
R. S. Hille 2/25/74

<b>NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT</b>		NDA NUMBER
		DATE APPROVAL LETTER ISSUED <b>MAR 11 1974</b>
TO:  Press Relations Staff (PA-40)	FROM:  <input checked="" type="checkbox"/> Bureau of Medicine <del>XXXXX</del> <b>Drugs</b>  <input type="checkbox"/> Bureau of Veterinary Medicine	
<b>ATTENTION</b> 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 <input checked="" type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> ABBREVIATED ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO NDA		CATEGORY <input type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG <b>SINEQUAN (doxepin hydrochloride)</b>		
DOSAGE FORM <b>ORAL CONCENTRATE</b>		HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> 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.)  <b>doxepin hydrochloride, 10 mg./cc.</b>		
NAME OF APPLICANT (Include City and State) <b>Pfizer, Inc. New York, New York</b>		
PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY <b>tranquillizer/antidepressant</b>		
<b>COMPLETE FOR VETERINARY ONLY</b>		
ANIMAL SPECIES FOR WHICH APPROVED		
<b>COMPLETE FOR SUPPLEMENT ONLY</b>		
CHANGE APPROVED TO PROVIDE FOR		
FORM PREPARED BY <i>William C. Crabbs</i> <b>William C. Crabbs, Consumer Safety Officer</b>		DATE <b>February 20, 1974</b>
FORM APPROVED BY <b>Robert C. Shultz, Supervisory Chemist</b>		DATE

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**LABELING**

APPROVED MAR 7 1974 37-2

Pfizer

# Sinequan<sup>®</sup>

## doxepin HCl

### CAPSULES ORAL CONCENTRATE

Pfizer

*WLL*

#### DESCRIPTION

SINEQUAN (doxepin HCl) is a new dibenzoxepin psychotherapeutic agent with marked antianxiety and significant antidepressant activity.

#### CHEMISTRY

SINEQUAN is a dibenzoxepin derivative and is the first of a new family of psychotherapeutic agents. Specifically, it is an isomeric mixture of N,N-Dimethyl-dibenz(b,e)oxepin- $\Delta^{11(6H)}$ ,  $\gamma$  propylamine hydrochloride.



#### INDICATIONS

In a carefully designed series of controlled studies, SINEQUAN has been shown to have marked antianxiety and significant antidepressant activity. SINEQUAN is recommended for the treatment of:

1. Patients with psychoneurotic anxiety and/or depressive reactions.
2. Mixed symptoms of anxiety and depression.
3. Alcoholic patients with anxiety and/or depression.
4. Anxiety associated with organic disease.
5. Psychotic depressive disorders including involutional depression and manic-depressive reactions.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, insomnia, guilt, lack of energy, fear, apprehension and worry.

In those patients in whom anxiety masks the depressive state, SINEQUAN is of particular value since it exerts a potent antidepressant effect as well as antianxiety activity.

Patients who have failed to respond to other antianxiety or antidepressant drugs may benefit from treatment with SINEQUAN.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient.

In a large series of patients systematically observed for withdrawal symptoms, none were reported. This is consistent with the virtual absence of euphoria as a side effect and the lack of addiction potential characteristic of this type of chemical compound.

#### CONTRAINDICATIONS

SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention.

#### WARNINGS

##### Usage in Pregnancy

SINEQUAN has not been studied in the pregnant patient. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient, although animal reproductive studies have not resulted in any teratogenic effects (See Animal Toxicology).

##### Usage in Children

The use of SINEQUAN in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

##### MAO Inhibitors

Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

#### PRECAUTIONS

Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy.

Although SINEQUAN has significant tranquilizing activity, the possibility of activation of psychotic symptoms should be kept in mind.

Other structurally related psychotherapeutic agents (e.g., iminodibenzyls and dibenzocycloheptenes) are capable of blocking the effects of guanethidine and similarly acting compounds in both the animal and man. SINEQUAN, however, does not show this effect in animals. At the usual clinical dosage, 75 to 150 mg per day, SINEQUAN can be given concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At doses of 300 mg per day or above, SINEQUAN does exert a significant blocking effect. In addition, SINEQUAN (doxepin HCl) was similar to the other structurally related psychotherapeutic agents as regards its ability to potentiate norepinephrine response in the animal. However, in the human this effect was not seen. This is in agreement with the low incidence of the

Labeling: *Original*  
 NDA No: 17-518 *Rec'd. 11-6-73*  
 Reviewed by: *W. Blumhagen*

PRECAUTIONS (continued)

side effect of tachycardia seen clinically.

ADVERSE REACTIONS

Anticholinergic Effects: Dry mouth, blurred vision, and constipation have been reported. They are usually mild, and often subside with continued therapy or reduction of dose.

Central Nervous System Effects: Drowsiness has been observed. This usually occurs early in the course of treatment, and tends to disappear as therapy is continued.

Cardiovascular Effects: Tachycardia and hypotension have been reported infrequently.

Other infrequently reported side effects include extrapyramidal symptoms, gastrointestinal reactions, secretory effects such as increased sweating, weakness, dizziness, fatigue, weight gain, edema, paresthesias, flushing, chills, tinnitus, photophobia, decreased libido, rash, and pruritus.

DOSAGE

For most patients with illness of mild to moderate severity, a starting dose of 25 mg t.i.d. is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients an initial dose of 50 mg t.i.d. may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

Although optimal antidepressant response may not be evident for two to three weeks, anti-anxiety activity is rapidly apparent.

SUPPLY

SINEQUAN is available as capsules containing doxepin HCl equivalent to:

10 mg and 100 mg doxepin: bottles of 100, 1000, and unit-dose packages of 100 (10 x 10's).

25 mg and 50 mg doxepin: bottles of 100, 1000, 5000, and unit-dose packages of 100 (10 x 10's).

SINEQUAN Oral Concentrate is available in 120 ml bottles with an accompanying dropper calibrated at 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. Each ml contains doxepin HCl equivalent to 10 mg doxepin. SINEQUAN Oral Concentrate should be diluted with water or suitable juices just prior to administration. Preparation and storage of bulk dilutions is not recommended.

ANIMAL PHARMACOLOGY

The psychopharmacological profile of SINEQUAN combines marked tranquilizing activity — as measured by suppression of conditioned avoidance behavior in rodents and a slowing of the EEG in monkeys, with significant antidepressant activity—as measured by potentiation of the stimulating effects of amphetamine and by antagonism of the sedating effects of reserpine and tetrabenazine. Potent spasmolytic activity—as measured in tissue preparations using the spasmogens: histamine, serotonin, barium chloride and acetylcholine; and mild peripheral vasodilatory effects—as measured in femoral artery blood flow studies in dogs, contribute to the pharmacological profile of SINEQUAN. SINEQUAN is well absorbed and rapidly metabolized after oral administration.

ANIMAL TOXICOLOGY STUDIES

TOXICOLOGY STUDIES

1. Acute Toxicity	LD <sub>50</sub> DOSE mg/kg I.V.	LD <sub>50</sub> DOSE mg/kg ORAL
MICE	14.6 to 19.6	148 to 178
RATS	12.7 to 18.8	346 to 460

2. Subacute Toxicity

An oral 30 day, subacute toxicity study with doxepin was performed on mongrel dogs at levels of 25 and 50 mg/kg/day. Hematology, clinical chemistry, and urinalysis showed no abnormalities. There was no mortality in these animals during this period. At the 25 mg/kg level mild emesis and sedation were observed. At the 50 mg/kg level mild emesis, increased heart rate, miosis, sedation, and twitching were observed. In a series of subacute rodent toxicity studies at levels of 25 and 50 mg/kg/day, no mortality was observed.

3. Chronic Toxicity

The results of canine toxicity studies at levels of 25 and 50 mg/kg/day for 12 months showed no histopathological changes attributable to the drug. Dogs treated with SINEQUAN at 25 and 50 mg/kg/day for up to 12 months exhibited slight emesis, ptosis, sedation, and twitching.

Over a period of 18 months, SINEQUAN was fed to rats at dose levels of 100, 50, 25, and 5 mg/kg. Fatty metamorphosis of the liver was observed primarily in the male rats after 18 months of feeding SINEQUAN at 100 mg/kg, a finding also seen with certain other potent tricyclic drugs but is of no clinical significance. At this same dose level there was inhibition of body weight gain in the females.

At a dose level of 50 mg/kg, slight hepatic fatty metamorphosis was observed in a one year study. In an 18 month study, dose levels of 50 mg/kg or less were essentially free of adverse effects.

4. Reproductive Studies

In animals receiving SINEQUAN in doses up to 25 mg/kg/day for 8 to 9 months, no changes were observed in number of live births, litter size, or lactation. A decreased conception rate resulted when male rats were treated at a dose level of 25 mg/kg/day for prolonged periods of time. This effect has been shown to occur with other psychotherapeutic agents and is attributed to their effects on the central and/or autonomic nervous systems. Gross and microscopic examination of the offspring revealed no evidence of drug-related teratologic effects.

Manufactured by:

PFIZER PHARMACEUTICALS, INC.

BARCELONETA, P.R. 00617

Distributed by:

 LABORATORIES

Labeling: Original  
NDA No: 125-01-01  
Reviewed by: W. L. ...

REMOVED MAR 11 1974

NDC 0663-5100-7607

# Sinequan

doxepin HCl  
equivalent to  
**10 mg / ml**  
of doxepin

**ORAL  
CONCENTRATE**

**120 ml**

CAUTION: Federal law prohibits dispensing without prescription.

**Pfizer** Distributed by  
LABORATORIES  
Manufactured by  
Pfizer Pharmaceuticals, Inc., Barcelona, P.R. 00617

RECOMMENDED STORAGE  
STORE BELOW 86° F. (30° C.)

Concentrate should be diluted in water or suitable juices immediately prior to administration.

Calibrated Dropper Enc'd. *sd.*

READ ACCOMPANYING PROFESSIONAL INFORMATION

**USUAL DAILY DOSAGE**  
Mild to Moderate Symptomatology — 75 mg (7.5 ml) to 150 mg (15 ml).  
Severe Symptomatology — 150 mg (15 ml) to 300 mg (30 ml).

*WLL*

Labelling: *Original*  
NDA No: *17-510* *Rev 8*  
Reviewed by: *W. M. K. [Signature]*

APPROVED NDC 6663-5100-47 *WAP 7607* *1974*

# Sinequan

doxepin HCl  
equivalent to  
**10 mg / ml**  
of doxepin

**ORAL  
CONCENTRATE  
120 ml**

CAUTION: Federal law prohibits  
dispensing without prescription.

RECOMMENDED STORAGE  
STORE BELOW 86° F. (30° C.)

Concentrate should be diluted in water or suitable  
juices immediately prior to administration.  
*Calibrated Dropper Enclosed.*

READ ACCOMPANYING  
PROFESSIONAL INFORMATION

**USUAL DAILY DOSAGE**  
Mild to Moderate Symptomatology— 75 mg  
(7.5 ml) to 150 mg (15 ml).  
Severe Symptomatology— 150 mg (15 ml) to  
300 mg (30 ml).

*wcc*

 Distributed by  
**LABORATORIES**  
Manufactured by  
Pfizer Pharmaceuticals, Inc., Barceloneta, P.R. 00617

APPROVED MAR 11 1974

Labeling: Original

NDA No: 17-510 Re'd. 11-6-73

Reviewed by: W. L. ...

*W*

#406

RECOMMENDED  
STORAGE  
STORE BELOW  
86° F. (30° C.)

NDC 0663-5100-47

7607

**Sinequan**<sup>®</sup>  
doxepin HCl  
ORAL  
CONCENTRATE  
120 ml

READ ACCOMPANYING  
PROFESSIONAL  
INFORMATION

**USUAL DAILY DOSAGE**

Mild to Moderate  
Symptomatology —  
75 mg (7.5 ml) to  
150 mg (15 ml).  
Severe Symptomatology —  
150 mg (15 ml) to  
300 mg (30 ml).

Concentrate should be  
diluted in water or  
suitable juices  
immediately prior to  
administration.

Calibrated Dropper  
Enclosed.

7607

NDC 0663-5100-47

**Sinequan**<sup>®</sup>

doxepin HCl

equivalent to

**10 mg / ml**

of doxepin

**ORAL  
CONCENTRATE**

**120 ml**

**CAUTION: Federal law prohibits  
dispensing without prescription.**

Distributed by  
**Pfizer LABORATORIES**  
Manufactured by



Pfizer Pharmaceuticals, Inc., Barceloneta, P.R. 00617

**P F I Z E R**

**P F I Z E R**

APPROVED MAR 11 1974

Labeling: Original  
NDA No: 17-510 Re'd. 11-6-73  
Reviewed by: W. H. ... 2/20/74

#406

RECOMMENDED  
STORAGE  
STORE BELOW  
86° F. (30° C.)

NDC 0663-5100-47  
**Sinequan**<sup>®</sup>  
doxepin HCl  
ORAL  
CONCENTRATE  
120 ml

7607

READ ACCOMPANYING  
PROFESSIONAL  
INFORMATION

**USUAL DAILY DOSAGE**

Mild to Moderate  
Symptomatology—  
75 mg (7.5 ml) to  
150 mg (15 ml).  
Severe Symptomatology—  
150 mg (15 ml) to  
300 mg (30 ml).

Concentrate should be  
diluted in water or  
suitable juices  
immediately prior to  
administration.

Calibrated Dropper  
Enclosed.

NDC 0663-5100-47 7607

**Sinequan**<sup>®</sup>  
doxepin HCl  
equivalent to  
**10 mg / ml**  
of doxepin  
**ORAL  
CONCENTRATE  
120 ml**

**CAUTION: Federal law prohibits  
dispensing without prescription.**

Distributed by  
**Pfizer**  
LABORATORIES  
Manufactured by

Pfizer Pharmaceuticals, Inc., Barcelona, P.R. 00617

**P F I Z E R**

**P F I Z E R**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**SUMMARY REVIEW**

*Orig*

SUMMARY OF NDA 17-516

Date Completed: 11/26/73  
NDA # 17-516  
Pfizer Pharmaceuticals  
Barcelonetta, Puerto Rico 00617

Name of Drug: (Trade) : Sinequan Oral Concentrate  
Generic: doxepin HCl

Dosage Form and Route of Administration: Oral Concentrate 10 mg/cc.

Category: Antianxiety and antidepressant.

Date of NDA: July 24, 1973  
Amended: November 2, 1973

Material Reviewed: Vol. 1.1 of NDA 17-516  
Amendment of November 2, 1973.

Clinical Evaluation:

The data to support claims for safety and efficacy consist of a crossover bioavailability investigation comparing the Sinequan Oral Concentrate with Sinequan Capsules (NDA 16-798) conducted by Milton Cohn, M.D., Research Testing Association, 1930 Chestnut Street, Philadelphia, Pa. at Eastern College, St. Davids, Pennsylvania. A review follows:

Review of Study by Cohn:

Problem: To establish the clinical equivalence of Sinequan Oral Concentrate to Sinequan Capsules.

Study Plan

Method:

Open: multiple cross-over N=18 ( 3 groups of 6 each )

Drugs:

Doxepin 50 mg. capsules.

Doxepin HCl liquid concentrate in 125 cc H<sub>2</sub>O

Doxepin HCl liquid concentrate in 125 cc orange juice.

Administration

Day 1 - each group of 6 received one study drug.

Day 2-7 Washout

Day 8 - crossover

Day 9-14 Washout

Day 15 - crossover.

Subject selection:

Healthy males 18-25 years of age and 135-200 lbs. weight.

No psychoactive drugs for 1 month and no drugs for 7 days.

Informal written consent.

## Procedure

Drugs (100 mg) given at the same time of day each study day.  
Samples taken at 0, 1, 2, 3, 5, 8 and 12 hours on Days 1, 8, 15  
sufficient to supply 10 ml of plasma.

Laboratory safeguards were provided.

Adverse reactions were recorded.

Results: According to the summary submitted by the sponsor the results of the study demonstrate the bioequivalence of the three dosages administered. It was claimed that there were no significant differences in the plasma levels of doxepin.

Drowsiness was reported by all subjects at comparable degrees of severity. The deviations in laboratory values were so small as to be without significance.

Comment: Claims for effectiveness and safety are based on the plasma levels of doxepin in the three experimental groups. The results are to be evaluated by bioavailability unit of the Bureau.

Amendment of November 2, 1973.

This submission has to do with the labeling for the Sinequan and contains a package insert with prescribing directions for use of both forms (capsules and concentrate) of the drug. A review of the new version of the prescribing information reveals that it is identical with the approved labeling for the capsule form (NDA 16-798) except for the inclusion of the oral concentrate information in the SUPPLY section and the change of date to October 1973.

## Conclusions

The review of the bioavailability information will determine whether or not the NDA is approvable.

There are no clinical studies presented as a basis for safety and efficacy.

This product is an additional dosage form of an approved drug.

Recommendation: Approval of the NDA if the results from the Cohn study as analyzed by the sponsor are confirmed by FDA bioavailability reviewers.

*Irma B. Hobart M.D.*  
Irma B. Hobart, M.D.

Orig.

Dup.

HFD-100

HFD-120

HFD-120/IHobart/11/26/73

FT/fkp/11/30/73

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**CHEMISTRY REVIEW(S)**

Orig

CHEMIST REVIEW OF NDA 17-516  
Review # First

NDA 17-516

Date Completed: 9/12/73

Sponsor: Pfizer Pharmaceuticals  
Pfizer Inc.  
235 East 42nd Street  
New York, N. Y. 10017

A. F.# 12-118

Product name:

Proprietary: Sinequan Oral Concentrate

Non-proprietary: doxepin hydrochloride

USAN: doxepin hydrochloride

Dosage Forms :

Rx

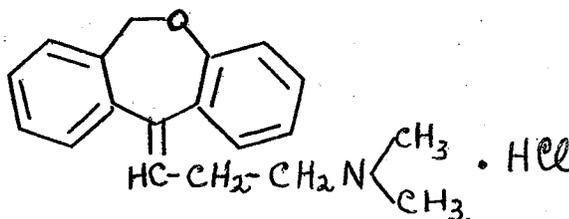
Oral Concentrate  
10 mg/cc

Pharmacological Category and/or Principal indication:

Antianxiety and antidepressant agent

Structural Formula and Chemical Name: N,N-Dimethyl-dibenz(b,e) oxepin  
 $\Delta^{11(\text{CH})}$   $\gamma$ -propylamine hydrochloride, cis-trans isomer mixture.

I



Initial Submission:

July 24, 1973

Supporting Inds: IND 6737, NDA 16-798 Sinequan(doxepin hydrochloride)  
NDAs Capsules, approved 9/23/69

Related Documents: DMF \_\_\_\_\_

b(4)

Conclusions and/or Recommendations: This NDA is unsatisfactory  
from the standpoint of manufacturing controls for the following

NDA 17-516

1 a

areas: Laboratory controls on the finished dosage form,  
insufficient stability data, lack of reference samples to be  
used for validation of methods, unsatisfactory draft labels,  
and clarification of the methodology used to show bioequivalence.

*Rachel S. Silk* 9-20-73  
Rachel S. Silk

Orig.  
Dup.  
BD-100  
BD-120  
BD-120/RSSilk/9/12/73  
Init/RSShultz/9/12/73  
FT/fkp/9/18/73

11 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

*Orig*

CHEMIST REVIEW OF NDA 17-516  
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
CHEMIST'S REVIEW #2

A. 1. NDA #17-516

Date Completed: 10-3-73

Sponsor: Pfizer Pharmaceuticals, Pfizer Inc.  
235 East 42nd Street  
New York, New York 10017

AF #12-118

2. Product Name(s):

Proprietary: Sinequan Oral Concentrate

Non-proprietary: doxepin hydrochloride

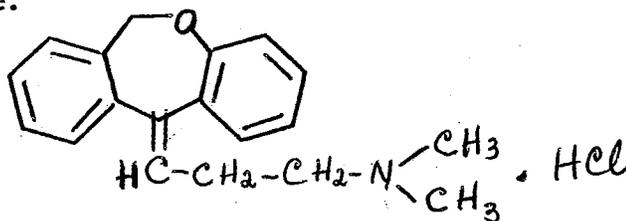
3. Dosage Form(s) and Route(s) of Administration: Oral Concentrate  
Contg. 10 mg/cc

Rx or OTC: Rx

4. Pharmacological Category and/or Principal Indication:

Antianxiety and antidepressant agent

5. Structural Formula and Chemical Name(s): N, N-dimethyl-  
dibenz (b,e) oxepin $\Delta^{11}$ (6H) gamma propylamine hydrochloride, cis-  
trans isomer mixture.



B. 1. Initial Submission: July 24, 1973

2. Amendments: September 27, 1973

3. Supporting IND, NDA, MF, and Letters of Authorization: IND 6737,  
NDA 16-798 Sinequan (doxepin hydrochloride) Capsules, approved  
9-23-69.

4. Related Documents (IND's, NDA's, etc): DMF \_\_\_\_\_ b(4)

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

15. Labeling: Unsatisfactory with comment:  
(NDA 4)

Although a statement has been included that the final printed labeling will include the equivalency statement on the main (front) panel as requested, the actual draft labels showing this revision have not been submitted.

*Rachel S. Silk* 11-15-73  
Rachel S. Silk  
Chemist

Orig.

Dup

BD-100 BD-120

BD-120/RSilk

F/T:ls:11/14/73

Init:RShultz/11/6/73

Tring

CHEMIST REVIEW OF NDA 17-516

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CHEMIST'S REVIEW #3

A. 1. NDA #17-516

Date Completed: 11-1-73

Sponsor: Pfizer Pharmaceuticals  
Pfizer, Inc.  
235 East 42nd Street  
New York, New York 10017

AF #12-118

2. Product Name(s):

Proprietary: Sinequan Oral Concentrate

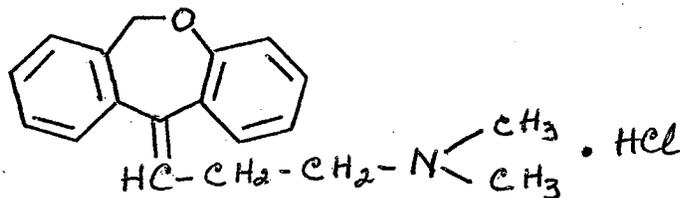
Non-proprietary: doxepin hydrochloride

3. Dosage Form(s) and Route(s) of Administration: Oral Concentrate  
Contg. 10 mg/cc

Rx or OTC: Rx

4. Pharmacological Category and/or Principal Indication: Anti-anxiety and antidepressant agent.

5. Structural Formula and Chemical Name(s): N, N - Dimethyl - dibenz (b,e) oxepin  $\Delta^H$  (6H) gamma propylamine hydrochloride, cis-trans isomer mixture.



B. 1. Initial Submission: July 24, 1973

2. Amendments: October 25, 1973

3. Supporting IND, NDA, MF, and Letters of Authorization: IND 6737, NDA 16-798 Sinequan (doxepin hydrochloride) Capsules, approved 9-23-69.

4. Related Documents (IND's, NDA's, etc): DMF \_\_\_\_\_

DMF # \_\_\_\_\_

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**PHARMACOLOGY REVIEW(S)**

*Orig*

December 28, 1973

PHARMACOLOGIST REVIEW OF NDA 17-516  
Original Summary

Sponsor: Pfizer Pharmaceuticals  
New York, New York 10017

Drug: Sinequan (doxepin HCl) oral concentrate

Formulation: Concentrate containing per ml:

[ doxepin HCl (= 10 mg. drug base) ]

b(4)

Recommended Dosage: 75-150 mg/day in divided dosage diluted with water or "suitable juices" just prior to administration.

Preclinical Data: None pertaining to this application; all relevant animal studies filed in this sponsor's NDA 16-798 for Sinequan capsules.

Labeling: The Package Insert is identical to that current for Sinequan capsules with the addition of information in the Dosage and Supply sections describing the concentrate.

Evaluation: The animal data in NDA 16-798 for Sinequan capsules adequately support approval for this same drug in the new formulation; there are no new or unusual excipients in the concentrate to warrant the need for additional preclinical testing.

A bioequivalence study in humans (concentrate vs capsules) has been submitted to this NDA and reviewed by the Bioavailability Group in our Clinical Research Branch.

In view of current Bureau recommendations for labeling revisions, appropriate changes in the proposed Package Insert seem timely.

Recommendations: Approved pending revision of the labeling to conform to current Bureau recommendations, i.e., addition of Actions (or Clinical Pharmacology) section, deletion of the Animal Pharmacology section.

Since Sinequan has now been on the market for 4 years in this country the appropriateness of calling this drug a dibenzoxepin (Description section) can be questioned.

b(4)

*Vera C. Glocklin*  
Vera C. Glocklin, Ph.D.

Orig  
HFD-100

Dup.  
HFD-120

FT/fkp/1/8/74  
HFD-120/YCG/12/28/73

January 25, 1974

SUMMARY OF BASIS OF APPROVAL NDA 17-516  
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

VI. Controls

Section 505(b)(2,3) Components and Composition: Satisfactory

Components are listed, unit and a batch formula are given for the oral concentrate containing 10 mg/cc.

Section 505(b)(4a,b) Facilities and Personnel: Satisfactory

Sinequan (doxepin hydrochloride) Oral Concentrate will be manufactured, processed, packaged and labeled at: \_\_\_\_\_  
\_\_\_\_\_ covers this facility. New drug substance is also made at \_\_\_\_\_

b(4)

(4c) Synthesis: Satisfactory

The synthetic process for doxepin hydrochloride was described in approved NDA 16-798, (for capsules). Modifications in the process were approved on July 13, 1971 (S-005).

(4d,e) Raw Material Controls: Satisfactory

Adequate specifications and tests for the active ingredient and the inert raw materials used in the dosage form have been provided.

(4f) Other Firms: Satisfactory. None mentioned.

(4g,h,j,k) Manufacturing and Processing: Satisfactory

Details provided, reference is also made to their DMF \_\_\_\_\_

b(4)

(4i) Container: Satisfactory

The oral, liquid concentrate will be packaged in a 4 oz. amber, glass bottle. A conventional screwcap will be used. Sampling and testing of bottles and closures were described.

(4l) Packaging and Labeling: Satisfactory

(4n) Laboratory Controls: Satisfactory

Sampling is adequate as per amendment of 10-25-73. Reference is made to DMF \_\_\_\_\_ Specifications and tests including identification and assay have been provided. Samples were sent to the \_\_\_\_\_ and to the Division of Drug Chemistry, O.P.R.T. for validation. Although \_\_\_\_\_ District experienced some difficulty

b(4)

with the \_\_\_\_\_ procedures used for identification, methods of ~~analyses~~ <sup>assays</sup> were judged to be suitable for control and regulatory purposes. b(4)

A statement and comments dated Jan. 29, 1974 have been submitted by Robert Stark, HFD-420, Drug Standards Research Branch.

(4p) Stability: Satisfactory for a 2 years expiration date.

Stability data for three lots of Sinequan Oral Concentrate which cover storage for 6 months at 30° C and for shorter periods under conditions of accelerated temperature, have been submitted. The retention values ranged from 98% to 103% of initial assay values. The concentrate was examined for doxepin content and for potential degradation product by \_\_\_\_\_ and by \_\_\_\_\_ respectively. For assay, the drug was

[  
d:  
]

(5) Samples: Satisfactory

Appropriate samples and analytical data have been provided for the new drug substance and concentrate. Methods have been validated in our laboratories, although \_\_\_\_\_ experienced some difficulty with the \_\_\_\_\_ procedures. (See under 4n, above).

(6) Labeling: Satisfactory for draft, immediate container labels for trade packages.

Establishment Inspection: Satisfactory

Please see memo from Clifford G. Broker dated 9-21-73.

Registration: Firm is registered.

Conclusion: Application is approvable from standpoint of manufacturing controls.

Rachel S. Silk  
Rachel S. Silk  
Chemist

Orig.  
Dup  
HFD-100  
HFD-120 HFD-120/RSSilk/  
HFD-120/Init:RShultz/1/28/74  
F/T:ls:1/29/74

Sinequan (doxepin HCl)  
Oral Concentrate 10 mg/ml  
NDA 17-516

Pfizer Pharmaceuticals  
AF 12-118  
Submission July 24, 1973

REVIEW OF A BIOAVAILABILITY STUDY

1. Submitted is a bioavailability study on the above product with Sinequan capsules 50 mg. as the reference product. The study was a three-way crossover since there was a third group of subjects that were given the drug with 125 ml of orange juice instead of water. Nine subjects were used. The dose was 100 mg. and the crossovers were done seven days apart. Blood samples were taken at 0, 1, 2, 3, 5, 8, and 12 hours after drug administration. The assay was a \_\_\_\_\_ with a lower limit of sensitivity of about 10 ng/ml. The study was done at \_\_\_\_\_ in \_\_\_\_\_

b(4)

2. The absorption and metabolism of the drug was quite variable from subject to subject. The peak blood levels occurred at two hours and averaged 44 and 54 ng/ml for the capsules and concentrate respectively. The respective areas under the curves averaged 341 and 374 ng-hr/ml. The serum half-life was about 5 hours. The orange juice evidently lowered the rate of absorption but had little effect on the total amount absorbed as the average peak value was 38 ng/ml and the area was 386 ng-hr/ml. Analysis of variance revealed no significant differences in the two products, but the power of the test, is very low.

3. The data was discussed with the Medical Officer familiar with this drug, Dr. Hobart. She said that the effective blood levels of this drug are unknown, but most probably it has a wide range.

RECOMMENDATION:

Although the data obtained in this study is not as precise as we like to see, the blood levels appear to be within the range of clinical effectiveness. It is, therefore, recommended that the study be accepted as evidence that the doxepin in the concentrate is bioavailable.

*Harold R. Murdock*  
Harold R. Murdock, Ph.D.  
Clinical Research Branch/DCR

cc: ~~NDA Orig.~~ Dup., Trip., HFD-200, HFD-220, HFD222, HFD-106, AF FILE,  
HFD-120 (R. Gregario)

HRMURDOCK/lj 1/8/74  
R/D init. by JPSKELLY

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**17-516**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

TO : BD-105  
ATTN: Stanley Stringer

DATE: September 21, 1973

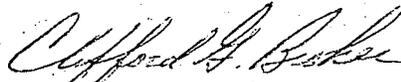
FROM : BD-340

SUBJECT: Approval of NDA 17-516, Sinequan Oral Concentrate

Applicant: Pfizer Pharmaceuticals, New York, NY

Manufacturer: Pfizer Pharmaceuticals, Barceloneta, P.R.

Based on our evaluation of the above manufacturer's compliance with CGMP Regulations, we have no objection to your approval of subject NDA insofar as it relates to such compliance.

  
Clifford G. Broker

cc:  
NDA Orig. ✓  
NDA Dup.  
BD-105  
BD-145, Harrison  
VM-200  
BD-316  
BD-340, Log  
BD-340, Working File  
BD-340, Voth  
CA-226  
NYK-DO  
SJN-DO

RWVOTH:lr

BD - 106

11

NDA 17-516

AUG 1 0 1973

Pfizer Pharmaceuticals  
Pfizer, Inc.  
Attention: Edward J. Hross  
235 E. 42nd Street  
New York, New York 10017

Gentlemen:

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

Name of Drug	Sinequan (doxepin HCL) Oral Concentrate, 10 mg. /cc.
Date of Application:	July 24, 1973
Date of Receipt:	July 31, 1973

We will correspond with you further after we have had the opportunity to study the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

*Scoville 8/9/73*

Barrett Scoville, M.D.  
Deputy Director  
Division of Neuropharmacological  
Drug Products  
Office of Scientific Evaluation  
Bureau of Drugs

NYK-DO *TAKAYO 8/9/73*  
 Orig. / Dup  
 BD-100 BD-106 BD-244 BD-120  
 BD-120/WCCrabbs/8/2/73 *WCCrabbs 8/8/73*  
 BD-120/Dr. Hobart Dr. Glocklin RSilk  
 F/T:ls:8/8/73

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

TO : Phil Walters, M.D.  
Office of Scientific Evaluation (HFD-100)

DATE: FEB 21 1974

FROM : *Barrett Scoville 2/21/74*  
Barrett Scoville, M.D.  
Division of Neuropharmacological Drug Products (HFD-120)

SUBJECT: Sinequan (doxepin HCl) Oral Concentrate Labeling, NDA 17-516

We agree that the labeling for doxepin HCl needs updating and are reluctant to perpetuate "1969 type" labeling.

However, this drug has been approved for marketing as a capsule by Pfizer (NDA 16-798) and as capsules and tablets by SK & F and Pennwalt (NDA 16-987). All marketed forms of doxepin have essentially identical labeling.

We believe that the most sensible course of action is to handle revision of the labeling for all formulations and firms at the same time. At this late date we do not believe withholding approval of the concentrate dosage form is a viable regulatory option in view of the current marketing status of the other dosage forms.

The most important labeling issue with which we must deal concerns the mixed anxiety/depression claims. This problem has been given extensive consideration by this division and the Neuropharmacology Advisory Committee, and guidelines will be available soon which will resolve this issue.

Pfizer has made a written commitment to expeditiously undertake labeling revisions for the drug. In the interim and in view of Pfizer's commitment, we recommend approval of the oral concentrate forms.

PERSONALLY SUBMITTED BY

*E. J. Gross*  
*7/31/73*  
*Paul Chapman*



PHARMACEUTICALS

PFIZER INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

July 24, 1973

Dr. Barrett Scoville, Acting Director  
Divison of Neuropharmacological Drugs  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

RE: SINEQUAN (doxepin HCl) ORAL CONCENTRATE - SAMPLES

Dear Dr. Scoville:

We are herein submitting samples of Sinequan (doxepin HCl) Oral Concentrate, concomitant with the filing - under separate cover - of a New Drug Application for this new dosage form of Sinequan.

Attached are 12 bottles, 120 cc. each, of Sinequan (doxepin HCl) Liquid Concentrate, 10 mg./cc., Lot 7777-8-1.

Please add this information to the file for Sinequan Oral Concentrate.

Thank you very much.

Sincerely,

*David C. Oppenheimer*

David C. Oppenheimer  
Associate Director  
Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS

DCO: jr  
Enc.



*Samples rec'd in JRS*  
*7-31-73*

PERSONALLY SUBMITTED BY



*E. J. Diross*  
7/31/73

PHARMACEUTICALS

PFIZER INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

NEW DRUG APPLICATION

July 24, 1973

17-516

Dr. Barrett Scoville, Acting Director  
Division of Neuropharmacological Drugs  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20852

RE: SINEQUAN (doxepin HCl) ORAL CONCENTRATE 10 mg./cc.  
NEW DRUG APPLICATION

Dear Dr. Scoville:

Pursuant to Title 21 of the Code of Federal Regulations, Section 130.4, we are herein submitting, in triplicate, a New Drug Application for Sinequan (doxepin HCl) Oral Concentrate 10 mg./cc. This submission is being made on behalf of Pfizer Pharmaceuticals, Inc., Barceloneta, Puerto Rico 00617.

Since this NDA concerns a new dosage form of a recently approved New Drug, we refer you to the approved NDA for Sinequan Capsules (16-798) for information regarding the manufacture and control of bulk doxepin HCl, safety, efficacy, etc., in your review of the attached Application.

To substantiate the clinical equivalence of Sinequan Oral Concentrate to Sinequan Capsules, a crossover bioavailability investigation was conducted, as filed to IND 6737 on April 5, 1973.

This study, conducted by \_\_\_\_\_ was designed to determine sera levels of doxepin administered as Sinequan (doxepin HCl) Capsules and as Sinequan (doxepin HCl) Oral Concentrate. Data from this study, a summary and statistical analysis are included in the section tabbed: "Clinical (Bioequivalency) Information." To facilitate your review, a copy of the clinical protocol filed to IND 6737 is also included.

b(4)

The labeling (package insert) for Sinequan Oral Concentrate is identical to that currently approved for Sinequan Capsules. The attached insert has been slightly modified to include the availability of, and dosing with, this new dosage form. All Indications, Warnings, Dosages, etc. remain as in the currently approved insert for Sinequan Capsules.



CONFIDENTIAL

Dr. Barrett Scoville, Acting Director

July 24, 1973

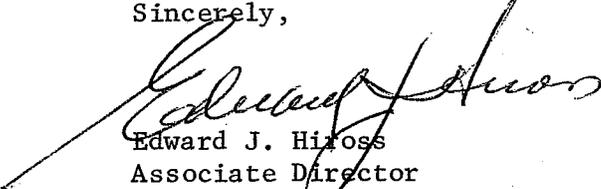
This drug will be available in a 120 cc. (4 oz.) bottle with a calibrated dropper. Package labeling has been appropriately designed and is also attached.

The results of accelerated stability studies on several lots of Sinequan Oral Concentrate are attached. Based on this 12 week data, we request approval of a 24 month expiration dating for this new dosage form.

The required Environmental Impact Analysis Report is attached to this submission and, as indicated, does not apply to this submission.

Should any questions arise during your review of this Application, please do not hesitate to call. Please communicate with me directly in assigning a file number for this New Drug Application.

Sincerely,



Edward J. Hirose  
Associate Director  
Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS

EJH: jr  
Attach.



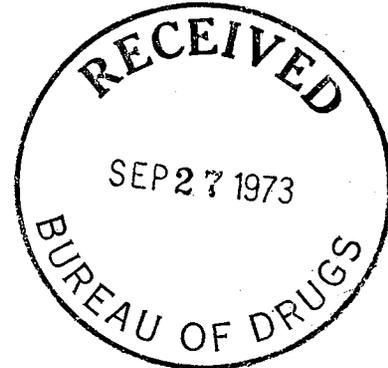
*Orig*

PHARMACEUTICALS

PERSONALLY SUBMITTED BY ~~THE~~ INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

*Dr. Michael A. Gaspador*  
*Rec'd by BAO*  
*9-27-73*

September 27, 1973



Dr. Barrett Scoville, Acting Director  
 Division of Neuropharmacological Drugs  
 Office of Scientific Evaluation  
 Bureau of Drugs  
 Food and Drug Administration  
 5600 Fishers Lane  
 Rockville, MD 20852

Re: NDA 17-516  
 Sinequan (doxepin hydrochloride) Oral Concentrate

Dear Dr. Scoville:

In a telephone conversation on September 12, 1973, Mrs. Rachel Silk of your Division discussed with Mr. Hiross of Pfizer Inc. our New Drug Application for Sinequan Oral Concentrate, NDA 17-516, filed on July 24, 1973. At that time, she indicated that there were some areas in the application which needed clarification. In response to her comments, we are herein submitting the following:

1. An Analysis of Doxepin and Demethyl Doxepin Blood Levels
2. Doxepin Blood Level Methodology
3. A Sampling Procedure - non-sterile liquids, certifiable and non-certifiable
4. Reference Samples of Doxepin Hydrochloride, Cis Isomer of Doxepin Hydrochloride and Trans Isomer of Doxepin Hydrochloride

<u>Compound</u>	<u>Identity</u>	<u>Quantity</u>
Doxepin Hydrochloride	93899-02EA	4 x 0.5 gm
<u>Cis</u> Isomer	3326-209-A	1 x 1.0 gm
<u>Trans</u> Isomer	6215-52-2	1 x 1.0 gm

*Samples rec'd in DRSS 9-27-73*

**CONFIDENTIAL**

*(2)*

September 27, 1973

5. Labeling - final printed labeling will include the Equivalency Statement on the front main panel.
6. Stability Data - the stability program described in NDA 17-516 for Sinequan liquid concentrate is continuing. Six month/30° C samples of the dosage form are scheduled to be taken for assay the first week of October. The assay results will be forwarded as soon as they become available.

If you require additional information, please contact me.

Please add this information to the file for Sinequan (doxepin hydrochloride) Oral Concentrate, NDA 17-516.

Sincerely,



Michael A. Hospador, Ph. D.  
Associate Director  
Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS

MAH:rp  
Encls.

*Memorandum*

TO : Rachel S. Silk, (HFD-120)  
Div. of Neuropharmacological Drug Products

DATE: January 29, 1974

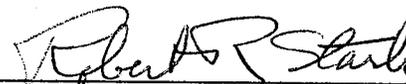
FROM : Chief, Drug Standards Research Branch (HFD-420)

SUBJECT: Laboratory Validation of Control Procedures  
NDA 17-516 Sinequan Oral Concentrate

Sinequan Oral Concentrate, Lot No. 7777-8-1, assayed: \_\_\_\_\_ mean 99.3) per cent of the labeled amount of doxepin by the firm's spectrophotometric method. The pH of the sample was 5.5. **b(4)**

The cis and trans isomers were identified in the concentrate by the firm's paper chromatographic method. The relative mobilities of the cis and trans isomers (with respect to the lower edge of the paper) were about 0.66 and 0.53, respectively.

The assay method is suitable for both control and regulatory analysis. The \_\_\_\_\_ identification is suitable for control purposes. We do not consider such methods suitable for regulatory methods because the field laboratories do not have chemists experienced in: \_\_\_\_\_ **b(4)**

  
Robert R. Stark



11 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative

ORIG

Rec'd 2-8-74

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

*MM 2/11*

TO : OFFICE OF PHARMACEUTICAL RESEARCH AND TESTING (BD-400)

DATE: February 4, 1974

→ *Mr. Stark HFD-420*

*TKS*  
*2/12/74*

FROM : Pharmaceutical Section (HFR-2162)

SUBJECT: NDA #17-516 Sinequan (doxepin HCl)  
Pfizer

Attached is the worksheet, \_\_\_\_\_ and \_\_\_\_\_ reporting our testing of the analytical control methods for the subject NDA.

b(4)

The methods appear satisfactory for their intended purpose.

*Ted M. Hopes*  
TED M. HOPES

cc: NYK-D60  
HFO-130 (w/copy of Form 2)  
File 463.36



14 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative

ORIG NEW CORRES

*Orig*

11



PHARMACEUTICALS

PFIZER INC., 235 EAST 42nd STREET, NEW YORK, N. Y. 10017

JOSEPH P. ATERNO  
Vice President  
Drug Regulatory Affairs  
and New Product Planning Division  
212 573-2556

February 19, 1974

Barrett Scoville, M.D., Acting Director  
Division of Neuropharmacological Drugs  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852

Re: Sinequan (doxepin HCl) Oral Concentrate  
NDA #17-516

Dear Dr. Scoville:

I refer you to a telephone conversation with Mr. William Crabbs of your Division relating to Sinequan (doxepin HCl) Oral Concentrate, NDA #17-516.

It is our understanding that the Sinequan Oral Concentrate will be approved providing that we make a commitment to revise the Sinequan package insert. We herein are making that commitment and hope that meetings with your Division can be arranged as soon as possible so that we may promptly undertake such a revision.

We will be in communication with your designee in the near future so that we may expedite the Sinequan Oral Concentrate approval and the package insert revision.



Sincerely yours,

J. P. Aterno, Vice President  
Drug Regulatory Affairs and  
New Product Planning Division

**CONFIDENTIAL**



PERSONALLY SUBMITTED

0716.

PHARMACEUTICALS

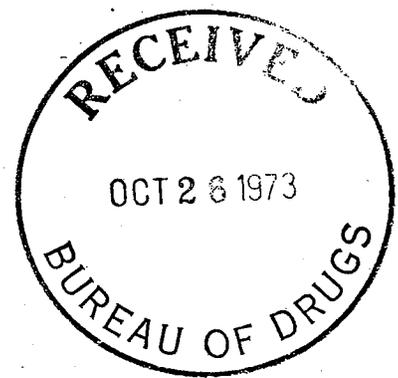
PFIZER, INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

PERSONALLY SUBMITTED BY

Michael A. Haspador, D.S.  
Rec'd by BAD  
10-26-73

October 25, 1973

Dr. Barrett Scoville, Acting Director  
Division of Neuropharmacological Drugs  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852



Re: NDA 17-516  
Sinequan (doxepin HCl) Oral Concentrate

Dear Dr. Scoville:

Pursuant to 21 CFR 130.9, we are herein submitting an Amendment to our Supplement to our New Drug Application for Sinequan Oral Concentrate, NDA 17-516, filed on July 24, 1973.

Herein is contained additional information as requested by Mrs. Rachel Silk and Dr. Harold Murdock:

1. Analytical Testing Data on Doxepin HCl Reference Samples. (Attachment 1)
2. Tabular Representation of Times for Drug Administration and Blood Sampling for all groups studied. (Attachment 2)
3. Bioavailability Study - Assay Sensitivity and Typical Gas Chromatographic Tracings. (Attachment 3)
4. Stability Report on Sinequan Liquid Concentrate (Attachment 4)
5. Curriculum Vitae for \_\_\_\_\_ conducted this study for determining the bioavailability of Sinequan Oral Concentrate, since the prior scheduling of numerous other projects to be performed internally by Pfizer Research did not permit us to use our capabilities for conducting this study. (Attachment 5)

CONFIDENTIAL

(2)

October 25, 1973

6. Sampling Procedures - Sinequan Oral Concentrate: Statistical Basis. This section includes sampling procedures for Non-Sterile Liquids, Certifiable and Non-Certifiable and Military Standard-105D. (Attachment 6)
7. Statistical Power of the Cahn Data. Using the approach outlined in Scheffe's, The Analysis of Variance, pp. 62-64, 1959, the power was calculated. The standard deviations used in the analysis were the ones obtained from the Latin Square Analysis; 152 for Areas under the curve and 5.85 for half-lives.

To detect a 100-unit difference (approximately 20%) on the Area Under the Curve data, the power was approximately .25 with a significance level of  $\alpha = .05$ . (The standard deviation was estimated as 152). For the half-life data, the power to detect a 1-unit difference (approximately 20%) was less than .20 with a significance level of  $\alpha = .05$ . The standard deviation was estimated as 5.85.

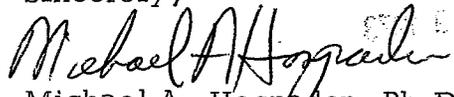
8. Labeling is being revised to include the Equivalency Statement and the Corporate Address on the main front panel. This labeling will be submitted to you when completed.
9. Subject Selection. 18 patients (in three groups) received 2 x 50 mg. capsules and 1 x 100 mg. oral concentrate (with either water or orange juice) in cross-over fashion. Sera samples from 9 subjects, 3 randomly selected from each group were subjected to chemical analysis. Samples from 9 randomly selected subjects rather than the entire 18 were assayed since, from a statistical viewpoint, the analysis of samples from all subjects would not have increased (or decreased) the validity of the data obtained using samples from 9 randomly selected individuals. It is our normal practice to include more subjects and to collect more samples than required to conduct a statistically valid, study. Thus for contingency purposes samples are available if confidence bounds exceed those anticipated.

Please add this information to the file for Sinequan (doxepin HCl) Oral Concentrate, NDA 17-516.

**CONFIDENTIAL**

MAH:rp  
Encls.

Sincerely,



Michael A. Hospedor, Ph.D.  
Associate Director

Drug Regulatory Affairs Division  
PFIZER PHARMACEUTICALS



PHARMACEUTICALS

PFIZER INC., 235 E. 42ND ST., NEW YORK, N.Y. 10017

FPL

Orig

November 2, 1973

Dr. Barrett Scoville, Acting Director  
Division of Neuropharmacological Drugs  
Office of Scientific Evaluation  
Bureau of Drugs  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20852

Re: NDA 17-516  
Sinequan (doxepin HCl) Oral Concentrate

Dear Dr. Scoville:

As indicated to you in my communication of October 25, 1973 concerning our Supplement to our New Drug Application, Sinequan Oral Concentrate, NDA 17-516, originally filed on July 24, 1973, I am forwarding to you revised labeling as part of that Supplement, as follows:

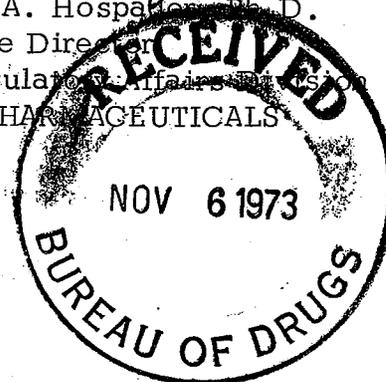
Label, I.C.	IBM 05-1942-37-0
Carton	IBM 10-1942-37-0
Package Insert	IBM 60-2135-37-2

Please include this labeling in our New Drug Application for Sinequan Oral Concentrate, NDA 17-516.

Sincerely,

*Michael A. Hospalen*

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MAH:rp  
Encls.

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