# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 020895

## CHEMISTRY REVIEW(S)

NOV 18 1997

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS
## Review of Chemistry, Manufacturing, and Controls

NDA #: 20,895 CHEM.REVIEW #: 1 REVIEW DATE: 10/15/97

| SUBMISSION | TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|---|
| ORIGINAL | 1P | 29-Sep-1997 | 30-Sep-1997 | 01-Oct-1997 |

NAME & ADDRESS OF APPLICANT: **Pfizer, Pharmaceutical Production Corp.**
Ringaskiddy
County Cork, Ireland

U.S. Agent Pfizer, Inc
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:

| | |
|---|---|
| **Proprietary:** | Viagra |
| **Nonproprietary/USAN/BAN:** | Sildenafil Citrate |
| **I.N.N.:** | Sildenafil |
| **Code Name/#:** | UK-92,480-10 |
| **CAS #** | 171,599-83-0 |
| **Chem.Type/Ther.Class:** | 1 P |

PATENT STATUS: 5,250,534, expires June 18, 2011

PHARMACOL.CATEGORY/INDICATION: Erectile Dysfunction

DOSAGE FORM: Tablets

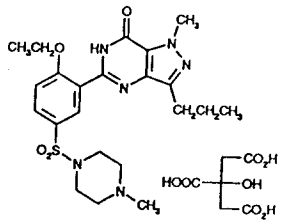
STRENGTHS: 25, 50, 100 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __x__ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1 H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine citrate



Sildenafil Citrate

Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ Molecular Weight Citrate: 666.7

Melting range 191-202°C Molecular Weight of Sildenafil: 474.6

SUPPORTING DOCUMENTS:

**RELATED DOCUMENTS (if applicable):** IND

**CONSULTS:** None

**REMARKS/COMMENTS:**

Viagra is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) and is indicated for the treatment of erectile dysfunction. The physiological mechanism responsible for erection of the penis involves the release of the nitric oxide (NO) in the corpus cavernosum in response to sexual stimulation. Nitric oxide activates the enzyme guanylate cyclase, which results in locally increased levels of cGMP, thereby producing smooth muscle relaxation. By inhibiting PDE5, VIAGRA enhances the normal physiological action of nitric oxide/cGMP, thereby allowing patients to obtain erection adequate for sexual intercourse.

EER is requested on 10/08/97.
Expiration date - 24 months in HDPE containers and blister packs.
Method validation will be requested to be performed by district laboratory.

**CONCLUSIONS & RECOMMENDATIONS:**
The firm has addressed to our recommendations that were made at the time of pre NDA meeting of 9/16/97. These were regarding strict controls for starting materials, identity tests, particle size specifications, impurity specifications particuarly toxicitv data for
present in the drug substance at data on I have highlighted the firm's actions in these regards in this review.
The information on following items will be obtained by communicating with the firm by telephone.

1) Partition coefficient data on drug substance
2) Data on IND product used in the clinical trials to support 24 months expiration date
3) Information on markers.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JAdvani/11/17/97
HFD-110/CSO
District
HFD-810/CHoiberg

R/D Init by: RWolters/

J.V. Advani, Review Chemist
filename: N20-895

11/18/97

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G. Buehler

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS
## Review of Chemistry, Manufacturing, and Controls

JAN 30 1998

**NDA #: 20-895** **CHEM.REVIEW #: 2** **REVIEW DATE: 01/09/98**

| SUBMISSION | TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|---|
| ORIGINAL | 1P | 29-Sep-1997 | 30-Sep-1997 | 01-Oct-1997 |
| Amendment | (BC) | 03-Dec-1997 | 04-Dec-1997 | 05-Dec-1997 |
| Amendment | (BC) | 19-Dec-1997 | 22-Dec-1997 | 29-Dec-1997 |

**NAME & ADDRESS OF APPLICANT:** Pfizer, Pharmaceutical Production Corp.
Ringaskiddy
County Cork, Ireland

U.S. Agent Pfizer, Inc
Eastern Point Road
Groton, CT 06340

**DRUG PRODUCT NAME:**

| | |
|---|---|
| **Proprietary:** | Viagra |
| **Nonproprietary/USAN/BAN:** | Sildenafil Citrate |
| **I.N.N.:** | Sildenafil |
| **Code Name/#:** | UK-92,480-10 |
| **CAS #** | 171,599-83-0 |
| **Chem.Type/Ther.Class:** | 1 P |

**PATENT STATUS:** 5,250,534, expires June 18, 2011

**PHARMACOL.CATEGORY/INDICATION:** Erectile Dysfunction

**DOSAGE FORM:** Tablets

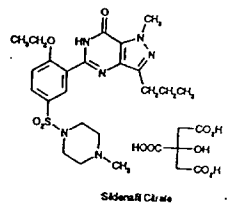
**STRENGTHS:** 25, 50, 100 mg

ROUTE OF ADMINISTRATION: Oral

**DISPENSED:** __x__ Rx _____ OTC

**STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

1-[4-Ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine citrate



Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ Molecular Weight Citrate: 666.7

Melting range 191-202°C Molecular Weight of Sildenafil: 474.6

SUPPORTING DOCUMENTS:

IND #

Drug Master Files:

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** None

**REMARKS/COMMENTS:**
Viagra is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) and is indicated for the treatment of erectile dysfunction. The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum in response to sexual stimulation. Nitric oxide activates the enzyme guanylate cyclase, which results in locally increased levels of cGMP, thereby producing smooth muscle relaxation. By inhibiting PDE5, VIAGRA enhances the normal physiological action of nitric oxide/cGMP, thereby allowing patients to obtain erection adequate for sexual intercourse.

EER was requested on 10/08/97. All establishments are acceptable.
Expiration date - 24 months in HDPE containers and blister packs.
A request for methods validation was sent to PHI-District lab. on 11/20/97.

Labeling and nomenclature committee as of 10/3/96, has provided provisional acceptance of the proprietary name pending final acceptance of the USAN name. The Sildenafil has been approved as the USAN name on 8/96.

**The amendments of 12/3/97 and 12/22/97 provide responses to telephone requests for information related to Chemist's Review #1.**

**CONCLUSIONS & RECOMMENDATIONS:**

The firm has responded to our recommendations that were made at the time of pre NDA meeting of 9/16/97. These were regarding strict controls for starting materials, identity tests, particle size specifications, impurity specifications particularly toxicity data for the present in the drug substance , data on This information was included in the original submission, and has been reviewed.

The information on the following items that was requested following review of the original submission, has now been obtained in these two amendments.

1) Partition coefficient data on drug substance
2) Data on IND product used in the clinical trials to support 24 months expiration date
3) Information on markers and amended dosage form monographs (DFMs) for sildenafil citrate tablets
4) Updated 6 months stability studies

Information supplied is reviewed, and found satisfactory.

Approvable

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JAdvani/01/27/98
HFD-110/CSO
District
HFD-810/CHoiberg

R/D Init by: JShort/

J.V. Advani, Review Chemist
filename: **N20-895**

1/30/98