

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **74745**

Trade Name **Megesterol Acetate Tablets USP 40mg**

Generic Name **Megesterol Acetate Tablets USP 40mg**

Sponsor Pharmachemie U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74745

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74745

APPROVAL LETTER

ANDA 74-745

Pharmachemie U.S.A., Inc.
U.S. Agent for: Pharmachemie B.V.
Attention: Hellen de Kloet
323 Davis Street
Northborough, MA 01532

FEB 27 1998



Dear Madam:

This is in reference to your abbreviated new drug application dated September 13, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Megestrol Acetate Tablets USP, 40 mg.

Reference is also made to your amendments dated July 1, 1996; December 30, 1997; and February 11, 17, and 24, 1998.

We have completed the review of this abbreviated 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 Division of Bioequivalence has determined your Megestrol Acetate Tablets USP, 40 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Megace[®] Tablets 40 mg of Bristol Myers Squibb). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

2/27/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74745

FINAL PRINTED LABELING

MEGESTROL ACETATE

TABLETS USP

APPROVED

WARNING

THE USE OF MEGESTROL ACETATE DURING THE FIRST 4 MONTHS OF PREGNANCY IS NOT RECOMMENDED.

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first 4 months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first 4 months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk of exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the

increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

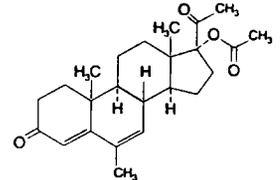
If the patient is exposed to megestrol during the first 4 months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

27 1998

DESCRIPTION

Megestrol acetate is a synthetic, antineoplastic and progestational drug. Megestrol acetate is a white, crystalline solid chemically designated as Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-, 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate. Solubility at 37°C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.52.

The molecular formula is $C_{27}H_{42}O_4$ and the structural formula is represented as follows:



PHARMACHEMIE B.V.
Postbus 552
2003 RN Haarlem

OPG Groep

1297.5v.KvH



Megestrol acetate is supplied as tablets for oral administration containing 40 mg megestrol acetate.

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, potato starch, and povidone.

CLINICAL PHARMACOLOGY

While the precise mechanism by which megestrol produces its antineoplastic effects against endometrial carcinoma is unknown at the present time, inhibition of pituitary gonadotropin production and resultant decrease in estrogen secretions may be factors. There is evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. The antineoplastic action of megestrol acetate on carcinoma of the breast is effected by modifying the action of other steroid hormones and by exerting a direct cytotoxic effect on tumor cells¹. In metastatic cancer, hormone receptors may be present in some tissues but not others. The receptor mechanism is a cyclic process whereby estrogen produced by the ovaries enters the target cell, forms a complex with cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and leads to the alteration of normal cell functions. Pharmacologic doses of megestrol acetate not only decrease the number of hormone-

dependent human breast cancer cells but also is capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested² that progestins may inhibit in one of two ways: by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, by interacting directly with the genome to turn off specific estrogen-responsive genes.

There are several analytical methods used to estimate megestrol acetate plasma levels, including mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC) and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay methods are about one-sixth those obtained by the GC method. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function^{1,3}.

Metabolites account for only 5% to 8% of the administered dose and are considered negligible³. The major route of drug elimination in humans is the urine. When radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 66.4%) and

fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). Respiratory excretion as labelled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.

It has been shown from bioavailability studies in normal male volunteers that oral absorption of megestrol acetate is variable. Plasma levels were assayed by high pressure liquid chromatography (HPLC). Peak levels range from 10 to 56 ng/mL when normalized to a 40 mg dose and the mean time to peak concentration ranged from 2 to 3 hours. Plasma elimination half-life is extremely variable and ranges from approximately 10 to 120 hours.

The steady state plasma concentrations for a 40 mg q.i.d. regimen have not been established.

INDICATIONS AND USAGE

Megestrol acetate tablets are indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (ie, recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.

CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. Megestrol ace-

tate tablets, are contraindicated as a diagnostic test for pregnancy.

WARNINGS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some male rat fetuses⁴. There are not adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

The use of megestrol in other types of neoplastic disease is not recommended.

See also "PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility" section.

Although the glucocorticoid activity of megestrol acetate has not been fully evaluated, laboratory evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in association with megestrol. Rare cases of clinically apparent adrenal suppression should be considered in any patient taking or withdrawing from chronic megestrol therapy who presents with symptoms of

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Carcinogenesis,
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with symptoms of

adrenal insufficiency such as hypotension, nau-
sea, vomiting, dizziness, or weakness. Laboratory
evaluation for adrenal insufficiency and replace-
ment stress doses of a rapidly acting glucocorti-
coid may be indicated for such patients.

PRECAUTIONS

General: Close surveillance is indicated for any
patient treated for recurrent or metastatic cancer.
Use with caution in patients with a history of
thromboembolic disease.

Use in Diabetics: Exacerbation of pre-existing
diabetes with increased insulin requirements has
been reported in association with the use of
megestrol.

Information for the Patients: Patients using
megestrol acetate should receive the following
instructions.

- 1. This medication is to be used as directed by
the physician.
- 2. Report any adverse reaction experiences while
taking this medication.

Laboratory Tests: Breast malignancies in which
estrogen and/or progesterone receptors are posi-
tive are more likely to respond to megestrol^{14,15}.

**Carcinogenesis, Mutagenesis, Impairment of
Fertility:** Administration of megestrol acetate to
female dogs for up to 7 years is associated with
an increased incidence of both benign and malign-

ant tumors of the breast¹⁶. Comparable studies in
rats and studies in monkeys are not associated
with an increased incidence of tumors. The rela-
tionship of the dog tumors to humans is unknown
but should be considered in assessing the benefit-
to-risk ratio when prescribing megestrol acetate
and in surveillance of patients on therapy^{18,19} (See
"WARNINGS" section).

Pregnancy: Pregnancy category D.
See "WARNINGS" section.

Nursing Mothers: Because of the potential for
adverse effects on the newborn, nursing should
be discontinued if megestrol is required for treat-
ment of cancer.

Pediatric Use: Safety and effectiveness in pedi-
atric patients have not been established.

ADVERSE REACTIONS

Weight Gain: Weight gain is a frequent side
effect of megestrol^{17,19}. This gain has been asso-
ciated with increased appetite and is not neces-
sarily associated with fluid retention.

Thromboembolic Phenomena: Thromboem-
bolic phenomena including thrombophlebitis and
pulmonary embolism (in some cases fatal) have
been reported.

Glucocorticoid Effects: See "WARNINGS" and
"PRECAUTIONS" sections.

Other Adverse Reactions: Heart failure, nausea
and vomiting, edema, breakthrough menstrual
bleeding, dyspnea, tumor flare (with or without
hypercalcemia), hyperglycemia, glucose intoler-
ance, alopecia, hypertension, carpal tunnel syn-
drome, mood changes, hot flashes, sweating and
rash.

OVERDOSAGE

No serious unexpected side effects have resulted
from studies involving megestrol acetate adminis-
tered in dosages as high as 1600 mg/day. Oral
administration of large, single doses of megestrol
acetate (5 g/kg) did not produce toxic effects in
mice⁴. Megestrol acetate has not been tested for
dialyzability; however, due to its low solubility it is
postulated that this would not be an effective
means of treating overdose.

DOSE AND ADMINISTRATION

Breast cancer: 160 mg/day (40 mg qid).
Endometrial carcinoma: 40 to 320 mg/day in
divided doses.

At least 2 months of continuous treatment is con-
sidered an adequate period for determining the
efficacy of megestrol acetate.

HOW SUPPLIED

Megestrol Acetate Tablets USP are available as
white, scored tablets with the imprint "MEGE-
STROL 40" containing 40 mg megestrol acetate.

NDC 0186-2170-78: package of
NDC 0186-2170-88: package of
NDC 0186-2170-05: child resis-
100.

**CAUTION: FEDERAL LAW PROHIBITS
SING WITHOUT PRESCRIPTION**

Storage
Store Megestrol Acetate Tablets in a cool, dry
room temperature 15 °C - 30 °C. Do not
protect from temperatures above 30 °C.

**Special Handling
Health Hazard Data**
There is no threshold limit value (TLV) for
OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels above the
recommended dosing levels or at levels above
effects described above (WARNING REACTIONS).
Women at risk of pregnancy should avoid such
exposure.

REFERENCES

- 1. Allegra, J.C., Kiefer SM: Mechanism of Action of
of Progestational Agents. *J Clin Oncol* 1985; 3
12 (Suppl 1): 3.
- 2. DeSombre ER, Kuivaneu M: Modulation of Estrogen-
Induced Protein Synthesis in the Endometrium.
Oncol 1985; 12 (Suppl 1): 6.

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with an increased incidence of tumors. The rela-
tionship of the dog tumors to humans is unknown
but should be considered in assessing the benefi-
to-risk ratio when prescribing megestrol acetate
and in surveillance of patients on therapy^{10,11} (See
"WARNINGS" section).

Pregnancy: Pregnancy category D.
See "WARNINGS" section.

Nursing Mothers: Because of the potential for
adverse effects on the newborn, nursing should
be discontinued if megestrol is required for treat-
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Pediatric Use: Safety and effectiveness in pedi-
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At least 2 months of continuous treatment is con-
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efficacy of megestrol acetate.

HOW SUPPLIED

Megestrol Acetate Tablets USP are available as
white, scored tablets with the imprint "MEGE-
STROL 40" containing 40 mg megestrol acetate.

NDC 0186-2170-78: package of 50 (10 strips of 5)
NDC 0186-2170-88: package of 100 (20 strips of 5)
NDC 0186-2170-05: child resistance container of
100.

**CAUTION: FEDERAL LAW PROHIBITS DISPEN-
SING WITHOUT PRESCRIPTION.**

Storage

Store Megestrol Acetate Tablets USP at controlled
room temperature 15 °C - 30 °C (59 °F - 86 °F);
protect from temperatures above 40 °C (104 °F).

Special handling

Health Hazard Data
There is no threshold limit value established by
OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels approaching
recommended dosing levels could result in side
effects described above (WARNINGS, ADVERSE
REACTIONS). Women at risk of pregnancy should
avoid such exposure.

REFERENCES

1. Allegra, JC, Kiefer SM: Mechanisms of Action
of Progestational Agents. *Semin Oncol*. 1985;
12 (Suppl 1): 3.
2. DeSombre ER, Kuivanen PC: Progestin
Modulation of Estrogen-Dependent Marker
Protein Synthesis in the Endometrium. *Semin
Oncol*. 1985; 12 (Suppl 1): 6.

- 5
3. Alexieva-Figusch J, Blankenstein MA, Hop WCJ, et al. Treatment of Metastatic Breast Cancer Patients with Different Dosages of Megestrol Acetate: Dose Relations, Metabolic and Endocrine Effects. *Eur J Cancer Clin Oncol*. 1984; 20: 33-40.
 4. Gaver RC, Movahhed HS, Farmen RH, Pittman KA. Liquid Chromatographic Procedure for the Quantitative Analysis of Megestrol Acetate in Human Plasma. *J Pharm Sci*. 1985; 74: 664.
 5. Cooper JM, Kellie AE. The Metabolism of Megestrol Acetate (17-alpha-acetoxy-6-methylprega-4,6-diene-3, 20-dione) in Women. *Steroids* 1968; 11: 133.
 6. David A, Edwards K, Fellowes KP, Plummer JM. Anti-ovulatory and Other Biological Properties of Megestrol Acetate. *J Reprod Fertil*. 1963; 5: 331.
 7. McGuire WL, Clark GM. The Prognostic Role of Progesterone Receptors in Human Breast Cancer. *Semin Oncol*. 1983; 10 (Suppl 4): 2.
 8. Horwitz KB. The Central Role of Progesterone Receptors and Progestational Agents in the Management and Treatment of Breast Cancer. *Semin Oncol*. 1988; 15 (Suppl 1): 14.
 9. Bonomi P, Johnson P, Anderson K, Wolter J, Bunting N, Strauss A, Roseman D, Shorey W, Econonou S. Primary Hormonal Therapy of Advanced Breast Cancer with Megestrol Acetate: Predictive Value of Estrogen Receptor and Progesterone Receptor Levels. *Semin Oncol*. 1985; 12 (1 Suppl 1): 48-54.
 10. Nelson LW, Weikel JH Jr., Reno FE. Mammary Nodules in Dogs During Four Years' Treatment with Megestrol Acetate or Chlormadinone Acetate. *J Natl Cancer Inst*. 1973; 51: 1303.
 11. Owen LN, Briggs MH. Contraceptive Steroid Toxicology in the Beagle Dog and Its Relevance to Human Carcinogenicity. *Curr Med Res Opin*. 1976; 4: 309.
 12. Ansfield FJ, Kallas GJ, Singson JP. Clinical Results with Megestrol Acetate in Patients with Advanced Carcinoma of the Breast. *Surg Gynecol Obstet*. 1982; 155: 888.
 13. Alexieva-Figusch J, Van Gilse HA, Hope WCJ, et al. Progestin Therapy in Advanced Breast Cancer: Megestrol Acetate - an Evaluation of 160 Treated Cases. *Cancer* 1980; 46: 2369.

DATE
December 1997

MANUFACTURED BY
PHARMACHEMIE BV
Haarlem, The Netherlands.

40 mg
MEGESTROL ACETATE TABLETS USP
100 Tablets

100 Tablets
MEGESTROL ACETATE TABLETS USP
40 mg

27 1998

APPROVED

Each tablet contains: Megestrol acetate 40 mg

Caution: Federal law prohibits dispensing without prescription.

This unit dose package is not child-resistant.

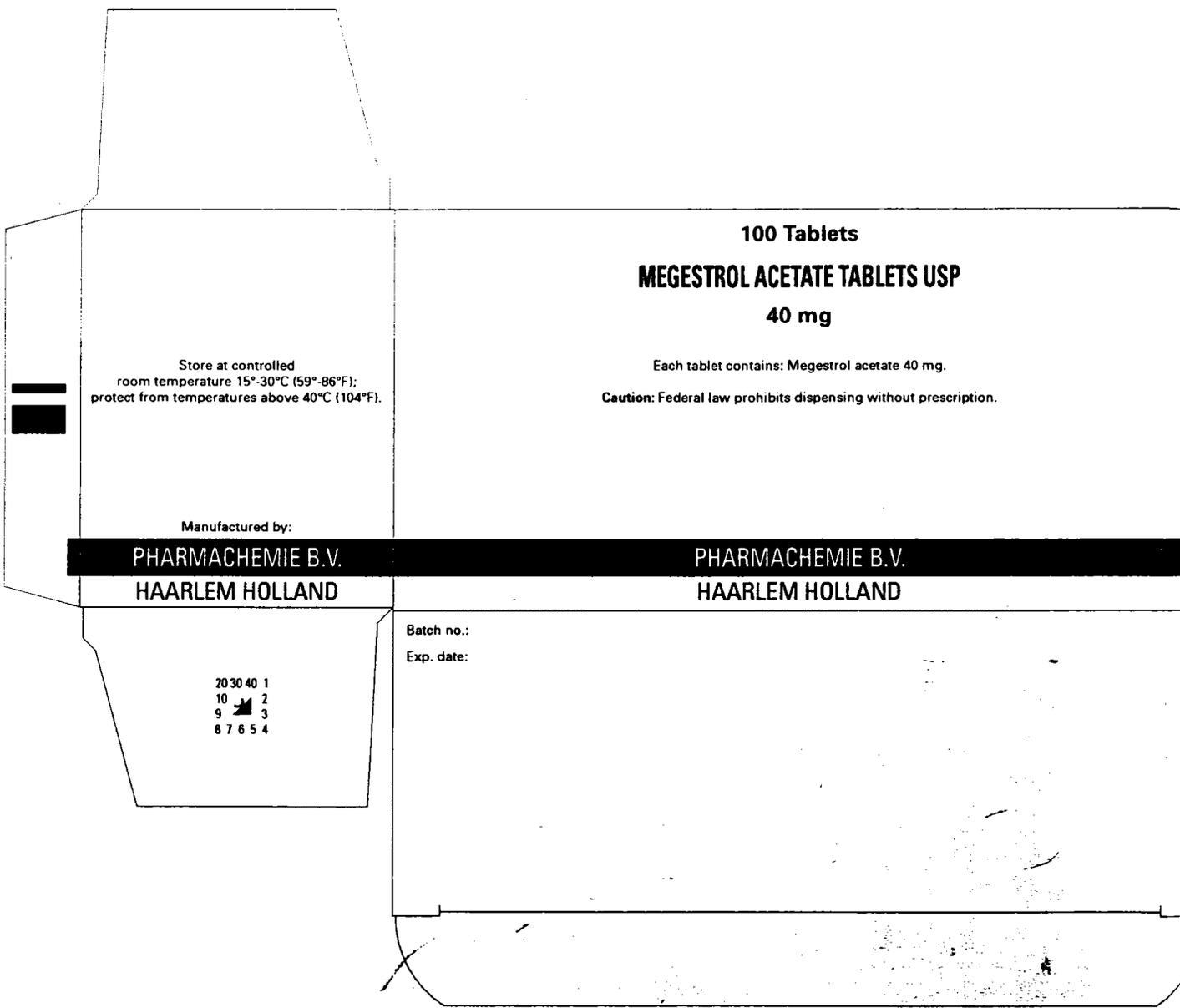
Usual dosage: See package insert.

Manufactured by:

PHARMACHEMIE B.V.
HAARLEM HOLLAND

PHARMACHEMIE B.V.
HAARLEM HOLLAND

PCH0070



100 Tablets

MEGESTROL ACETATE TABLETS USP

40 mg

Store at controlled
room temperature 15°-30°C (59°-86°F);
protect from temperatures above 40°C (104°F).

Each tablet contains: Megestrol acetate 40 mg.
Caution: Federal law prohibits dispensing without prescription.

Manufactured by:

**PHARMACHEMIE B.V.
HAARLEM HOLLAND**

**PHARMACHEMIE B.V.
HAARLEM HOLLAND**

203040 1
10 2
9 3
8 7 6 5 4

Batch no.:

Exp. date:



50 Tablets

MEGESTROL ACETATE TABLETS USP

40 mg

Each tablet contains: Megestrol acetate 40 mg.

Caution: Federal law prohibits dispensing without prescription.

PHARMACHEMIE B.V.

HAARLEM HOLLAND

This unit dose package is not child-resistant.

Usual dosage: See package insert.

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM, HOLLAND

2030 00 1
17
0
8 7 6 5 4

Batch no.:
Exp. date:

HAARLEM HOLLAND

PHARMACHEMIE B.V.

Caution: Federal law prohibits dispensing without prescription.

Each tablet contains: Megestrol acetate 40 mg.

40 mg

MEGESTROL ACETATE TABLETS USP

50 Tablets

Store at controlled room temperature 15°-30°C (59°-86°F);
protect from temperatures above 40°C (104°F).

Manufactured by:
PHARMACHEMIE B.V.
HAARLEM, HOLLAND

PCH0071

50 Tablets

MEGESTROL ACETATE TABLETS USP

40 mg

U.S. FOOD & DRUG ADMINISTRATION

APPROVED

MEGESTROL ACETATE TABLETS USP
100 Tablets
40 mg

100 Tablets
MEGESTROL ACETATE TABLETS USP
40 mg

Each tablet contains: Megestrol acetate 40 mg.

Caution:
Federal law prohibits dispensing without prescription.

Usual Dosage:
See package insert.

100 Tablets
MEGESTROL ACETATE TABLETS USP
40 mg

Each tablet contains: Megestrol acetate 40 mg.

Caution:
Federal law prohibits dispensing without prescription.

Store at controlled room temperature
15°-30°C (59°-86°F); protect from
temperatures above 40°C (104°F).

Keep out of the reach of children.

Dispense in a tight container
as defined in the USP.

Manufactured by:

PHARMACHEMIE B.V.
HAARLEM HOLLAND

PHARMACHEMIE B.V.
HAARLEM HOLLAND

PHARMACHEMIE B.V.
HAARLEM HOLLAND

PHARMACHEMIE B.V.
HAARLEM HOLLAND

20 20 40 1
10 2
9 3
8 7 6 5 4

Batch no.:
Exp. date:

PCH0074
APR 27 1998

PHARMACHEMIE B.V. - HAARLEM/ZAANDAM				
DATUM BINNENKOMST:	Q.A.	V.V.	Q.C.	IN

BASISTEKST	97.400.248
VERSIE	A
VERPAKKING	EAV

MEGESTROL ACETATE
 TABLET, USP
 40 mg
 Exp.: 00-0000
 PCH: 00 0 00 00
 Manufactured by:
 Pharmachemie B.V.
 Haarlem, Holland

MEGESTROL ACETATE
 TABLET, USP
 40 mg
 Exp.: 00-0000
 PCH: 00 0 00 00
 Manufactured by:
 Pharmachemie B.V.
 Haarlem, Holland

97.400.248

VANDOK ZAANDAM

7 1987

VANDOK ZAANDAM

Each tablet contains:
Megestrol acetate 40 mg.

Store at controlled room temperature
15°-30°C (59°-86°F); protect from
temperatures above 40°C (104°F).

Caution: Federal law prohibits
dispensing without prescription.

NDC 0188-2170-05

100 Tablets

**MEGESTROL ACETATE
TABLETS USP**

APPROVED 40 mg

Manufactured by:

PHARMACHEMIE B.V.
HAARLEM  HOLLAND

Usual dosage:
See package insert.

Warning: Keep out of the reach
of children.

Dispense in a tight container as
defined in the USP.

Batch no.: 27 1998

Exp. date:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74745

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW #3 ADDENDUM #1
2. ANDA 74-745
3. APPLICANT, Name:
Pharmachemie USA, Inc.
7. Non-PROPRIETARY Name: Megestrol Acetate Tablets USP, 40 mg
9. AMENDMENTS & Other Dates.
 - A. FIRM: *02-24-98 tel amendment responding to message of 2-23.
 - B. FDA: 02-23-98 telephone message from Dr. Rudman

Re CONTAINERS:

ADDENDUM: As the application stated p.938 that the firm may change the primary packaging components and manufacturer as it deems appropriated with concurrence from its management we told them 2-23-98 that this is not appropriate. In the tel. amendment of 2-24-98 this page was corrected as suggested & referred only to 314.70 as appropriate. sat.

STABILITY. ADDENDUM:

In a telecon with the firm 2-23-98 they were told that the phrase on p.1157, "annually, one production batch will be added to the stability program" should be corrected since there are two distinct packaging systems (unit dose and HDPE bottle). In the amendment of 2-24-98 (faxed) the firm corrected this to read, "annually, one production batch per package will be added...".

18. CONCLUSIONS & RECOMMENDATIONS:

AP

19. Reviewer

Robert W. Trimmer
BRANCH II, DIV. OF CHEMISTRY I, OGD
ADDENDUM 2-24-98

Technical Team Leader:

Michael J. Smela, Jr.

2-24-98

2/24/98

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1. CHEMIST'S REVIEW #3
2. ANDA 74-745
3. APPLICANT, Name/Address/Telephone/Fax:
Pharmachemie USA, Inc.
323 Davis Road
Northborough, MA 01532
☎ 508/393-0973 FAX 508/393-0974
4. Legal Basis for ANDA Submission: 505(j)
5. Supplement: n/a
6. PROPRIETARY Name: same
7. Non-PROPRIETARY Name: Megestrol Acetate Tablets USP,
40 mg
8. Supplement Provides For: n/a
9. AMENDMENTS & Other Dates.
 - A. FIRM:
 - 09-13-95 Orig. application
 - *12-29-97 minor amendment [*=new submission]
 - *02-05-98 telefon amendment
 - *02-11-98 telefon amendment
 - *02-12-98 telefon amendment (very minor)
 - B. FDA:
 - 11-10-97 NA letter
 - 12-16-97 Labeling review and Deficiencies
 - 01-27-98 Telephone message requesting tel. amendment.
 - 02-10-98 Telephone message requesting tel. amendment.
10. PHARMACOLOGICAL CATEGORY: For palliative treatment of
advance carcinoma of the
breast or endometrium.
11. Rx or OTC: Rx
12. RELATED ANDA's: -
Innovator's Product Name: Megace (Mead Johnson)
13. DOSAGE FORM: Tablets
14. POTENCY: 40 mg
15. CHEMICAL NAME: Pregna-4,6-diene-3,20-dione,
17-(acetyloxy)-6-methyl-.
16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:

The API and the drug product are USP. No QA file exists.

B. Firm's Response to the last Action Letter:

1.

Revised to cover every batch with 2/5/98 amendment.

2. Please be advised that Drug Master File _____ for the active ingredient is still deficient. The holder of the DMF has been notified.

Firm's Response:

acknowledged

COMMENT: The last review of _____ amendment & update was adequate.

3. We note that you have updated and incorporated the USP 23, Supplement 5, dissolution testing (75 rpm) as specified. Please provide data for your biobatch using the revised dissolution specifications, per USP 23 Apparatus 2 (paddle) at 75 rpms. Please commit to current USP testing for both

Firm's Response provided as follows:

USP 23 Apparatus II, paddle

900 mL of 1% sodium lauryl sulphate

at 75 rpm for 60 min. with NLT _____ (Q) of the labeled amt. being dissolved.

COMMENT:

sat

4. Please provide any additional available long term stability data for this product.

Firm's Response:

The firm provided updated stability data covering 24 mo. at 25 ± 2°C/60% RH ±5%

COMMENT:

sat.

5. The firm also acknowledged their obligations to comply with the methods and procedures in the USP for their DP. sat.

18. CONCLUSIONS & RECOMMENDATIONS:
AP Pending updated EER

19. Reviewer
Robert W. Trimmer
BRANCH II, DIV. OF CHEMISTRY I, OGD

Technical Team Leader:
Michael J. Smela, Jr.

Date Started: 1-21-98
Date Completed: 1-23-98
revised 2-12-98

2-18-98

2/19/98

EER update acceptable
on 11/5/97.

2/19/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74745

BIOEQUIVALENCE REVIEW(S)

OCT 25 1996

Megestrol Acetate Tablets USP, 40 mg
ANDA # 74-745
Reviewer: Hoainhon Nguyen
WP # 74745a.796

Pharmachemie USA
Oradell, New Jersey
Submission Date:
July 1, 1996

Review of a Study Amendment

The firm has amended the application in response to the deficiency letter issued by the Division of Bioequivalence on February 23, 1996.

The deficiencies are summarized below.

1. The submission lack of all standards, controls and subject samples of the study.
2. Stability study data are missing.
3. Dissolution testing was not in accordance with USP 23 procedure and specifications.
4. The composition of the test product is not submitted.

The firm's responses to the above deficiency comments are summarized below.

Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Pharmachemie on the test product, Megestrol Acetate Tablets USP, 40 mg, lot # WRD0047, comparing it with the reference product, Megace Tablets USP, 40 mg, lot# MAE29, has been found acceptable by the Division of Bioequivalence. The test product is bioequivalent to the reference product under fasting conditions.
2. The in-vitro dissolution testing conducted by Pharmachemie on its Megestrol Acetate Tablets USP, 40 mg has been found acceptable.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 1% SLS at 37°C using USP XXIII apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

Not less than _____ of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

10/11/96
Hoanhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

_____ 10/15/96

Concur: _____ Date: 10/17/96
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA # 74-745 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/10-09-96/WP # 74745a.796

Attachments: 4 pages

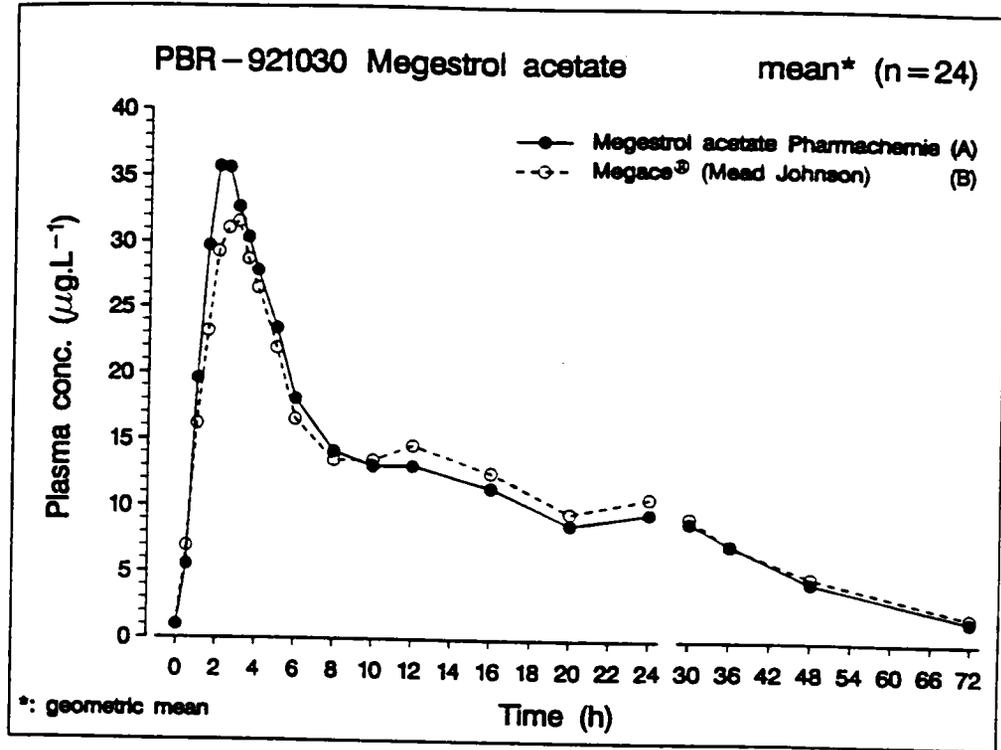


Figure 2.

Geometric mean plasma concentration profiles of megestrol acetate as observed after single dose oral administration of 80 mg of megestrol acetate to 24 subjects
 A = two 40 mg Megestrol Acetate (Pharmachemie B.V.) tablets
 B = two 40 mg Megace® (Mead Johnson) tablets

Table I

Megestrol Acetate Comparative Pharmacokinetic Parameters
n = 24; Dose = 80 mg

<u>Parameters</u>	<u>Pharmachemie's</u> <u>Geometric</u> <u>Mean</u>	<u>Megace^R</u> <u>Geometric</u> <u>Mean</u>	<u>90%</u> <u>C.I.</u>	<u>T/R</u> <u>Ratio</u>
AUC (0-T) ng.hr/ml	595.7	628.8	[0.88;1.02]	0.95
AUC (0-36) ng.hr/ml	480.2	493.2	[0.92;1.03]	0.97
AUC (0-Inf) ng.hr/ml	704.6	718.1	[0.91;1.06]	0.98
C _{MAX} (ng/ml)	40.46	39.25	[0.93;1.14]	1.03

WP# 74745 a. 796 Attachment 3 of 4

Table II
Comparative Mean Plasma Levels of Megestrol Acetate (n = 24)
ng/ml(CV)

Dose = 80 mg

<u>Hour</u>	<u>Pharmachemie's</u>	<u>Megace^R</u>
0	<2.00	<2.00
0.50	9.60(83)	14.95(94)
1.00	26.57(59)	24.19(72)
1.50	33.20(43)	29.63(59)
2.00	37.37(32)	32.82(45)
2.50	37.25(31)	33.35(36)
3.00	34.45(34)	33.09(32)
3.50	32.11(36)	30.51(36)
4.00	29.43(35)	28.37(39)
5.00	25.29(41)	23.86(41)
6.00	19.31(36)	17.57(34)
8.00	15.18(37)	14.47(34)
10.00	13.96(36)	14.17(34)
12.00	13.84(33)	15.14(27)
16.00	11.97(31)	13.07(28)
20.00	9.07(32)	10.07(33)
24.00	9.97(30)	11.35(35)
30.00	9.30(32)	10.22(45)
36.00	7.79(41)	8.21(60)
48.00	5.22(59)	5.63(61)
72.00	2.19(81)	2.52(82)
AUC(0-T)ng.hr/ml	625.0(34)	664.4(36)
AUC(0-36)ng.hr/ml	494.0(25)	507.9(25)
AUC(0-Inf)ng.hr/ml	741.6(36)	760.5(39)
C _{MAX}	42.00(27)	40.82(29)
T _{MAX} (hrs)	2.00	2.00
K _{EL} (1/hrs)	0.037(33)	0.038(29)
T _{1/2} (hrs)	20.44(33)	19.80(28)

Megestrol Acetate Tablets USP
40 mg

Amendment #1

SECTION VII

Composition Drug Product

Each tablet of Megestrol Acetate Tablets USP contains:

Megestrol acetate	USP + BP + Pharmachemie req.	40.00 mg
Potato starch	NF	
Lactose monohydrate	NF	
Povidone	USP	
Microcrystalline cellulose	NF	
Colloidal silicon dioxide	NF	
Magnesium stearate	NF	

		400.00 mg

Scaling up or minor changes in production may cause fluctuations in the amount of excipients as a percent of the total formula.

Development Pharmaceuticals

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74745

CORRESPONDENCE

323 Davis Street
Northborough
Massachusetts 01532
Telephone: (508) 393-0973
Fax: (508) 393-0974
email: pchusa@gis.net

PHARMACHEMIE U.S.A., INC.



teletax message

To : Office of Generic Drugs/CDER/FDA
Attn : Dr A. Rudman
Faxnumber : 301 594 0180
From : Hellen de Kloet
Date : February 24, 1998
Subject : **Megestrol Acetate Tablets, USP 40 mg ANDA 74-745
Telephone Amendment #6**
Cc : -
Number of pages : 13 (Including this page)

AMENDMENT

HJM

Dear Mr. Rudman,

Referring to our telephone conversation of February 23, 1998, please find attached Telephone Amendment #6 of the above mentioned product.

Three hard copies will be send to you by mail.

If you still have questions please contact me at : 508 393 0973.

Sincerely yours,

Hellen de Kloet

Hellen de Kloet
Vice President
Medical & Regulatory Affairs

MINUTES OF PHONE CALL

DATE: February 23, 1998

SUBJECT: ANDA 74-745, Megestrol Acet. Tabs

ORGANIZATION: Pharmachemie

PARTICIPANTS: Allen Rudman
Helen De Kloet

Helen returned my phone call from last week and was asked to clarify the following two statements in ANDA 74-745, Megestrol Acetate Tabs:

1. Page 938 of the application states says that the firm may change the primary packaging components and manufacturer as it deems appropriate with concurrence from its management.

Helen agreed that this was not appropriate and offered to amend the wording to conform with CFR 314.70 (d).

2. Page 1157 of the application states that "annually, one production batch will be added the stability program". There are, however, two distinct packaging configurations including a unit dose and an HDPE bottle.

Helen agreed to amend the wording to include the phrase "per packaging configuration" to the above sentence.

We agreed that the amendment should be submitted as a telephone amendment by fax.

12/30/97

ORIGINAL AMENDMENT

N/A

ANDA 74-745

MEGESTROL ACETATE TABLETS USP
40 mg

PHARMACHEMIE B.V.
HAARLEM, THE NETHERLANDS

RECEIVED

DEC 30 1997

GENERIC DRUGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

PHARMACHEMIE B.V.
HOLLAND
Form Approved: OMB No. 0910-0188
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER
ANDA 74-745

APPLICANT INFORMATION

NAME OF APPLICANT

Pharmachemie B.V.

DATE OF SUBMISSION

TELEPHONE NO. (Include Area Code)
+ 31 23 5147 147

FACSIMILE (FAX) Number (Include Area Code)
+31 23 5329 869

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Swensweg 5
NL-2031 GA Haarlem
The Netherlands

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Ms. Hellen de Kloet
Pharmachemie U.S.A. Inc.
323 Davis Street
Northborough, MA 01532
tel: 508 393 0973 fax: 508 393 0974

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Megestrol Acetate Tablets USP

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
see appendix

CODE NAME (If any)

DOSEAGE FORM:
Tablets

STRENGTHS:
40 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:

see appendix

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507 **RECEIVED**
DEC 30 1997

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Megace

Holder of Approved Application

Mead Johnson

GENERIC DRUGS

TYPE OF SUBMISSION
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

FDA deficiency letter dated November 10, 1997

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Pharmachemie B.V.

Swensweg 5

DMF nr. 8786

NL-2031 GA, The Netherlands all steps

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(b)s, IDEs, BMFs, and DMFs referenced in the current application)

see appendix

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

PHARMACHEMIE B.V.
HOLLAND
Form Approved: OMB No. 0901-0001
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER
ANDA 74-745

APPLICANT INFORMATION

NAME OF APPLICANT Pharmachemie B.V.	DATE OF SUBMISSION
TELEPHONE NO. (Include Area Code) + 31 23 5147 147	FACSIMILE (FAX) Number (Include Area Code) +31 23 5329 869
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Swensweg 5 NL-2031 GA Haarlem The Netherlands	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Ms. Hellen de Kloet Pharmachemie U.S.A. Inc. 323 Davis Street Northborough, MA 01532 tel: 508 393 0973 fax: 508 393 0974

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Megestrol Acetate Tablets USP	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) see appendix	CODE NAME (if any)	
DOSAGE FORM: Tablets	STRENGTHS: 40 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: see appendix		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED APPLICATION (21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	RECEIVED DEC 30 1997
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507	
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Megace Holder of Approved Application: Mead Johnson	GENERIC DRUGS
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER	
REASON FOR SUBMISSION FDA deficiency letter dated November 10, 1997	
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Pharmachemie B.V.
Swensweg 5 DMF nr. 8786
NL-2031 GA, The Netherlands all steps

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see appendix



PHARMACHEMIE U.S.A., INC.

323 Davis Street
Northborough
Massachusetts 01532
Telephone: (508) 393-0973
Fax: (508) 393-0974
email: pchusa@gis.net

telex message

To : Office of Generic Drugs/CDER/FDA
Attn : Dr B. Trimmer
Faxnumber : 301 594 0180
From : Hellen de Kloet
Date : February 11, 1998
Subject : **Megestrol Acetate Tablets, USP 40 mg ANDA 74-745**
Telephone Amendment #5

Cc : -
Number of pages : 25 (Including this page)

Dear Mr. Trimmer,

Referring to our telephone conversation of February 10, 1998, please find attached Telephone Amendment #5 of the above mentioned product.

Three hard copies will be send to you by mail.

If you still have questions please contact me at : 508 393 0973.

Sincerely yours,

Hellen de Kloet
Vice President
Medical & Regulatory Affairs

05/02 '98 15:37

31 23 5329 869

PHARMACHEMIE BV

001

Swensweg 5, Haarlem
P.O. Box 552
2003 RN Haarlem
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 879
Telex 41879 phchm nl
ABN AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 18 89 85

PHARMACHEMIE BV

Attn. Dr. B. Trimmer
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150

TELEFAX

To: 00 - 1 301 594 0180
From: + 31 23 5329 869
Number of pages: 45

Haarlem, February 5, 1998
Ref.: pcs/khn/0144/98

Subject : Megestrol Acetate Tablets, USP, 40 mg ANDA 74-745
Telephone Amendment #4

Dear Dr. Trimmer,

Referring to our telephone conversation, please find attached Telephone Amendment #4 in response to your telephone deficiency of January 27, 1998.

Please be informed that hard copies of this Telephone Amendment #4 will be forwarded to you by our USA agent, Ms. Hellen de Kloet.

Hoping to have informed you sufficiently, I remain,

Sincerely yours,
PHARMACHEMIE B.V.



Ms. P.C. Stokes
Director Regulatory Affairs

Cc.: Ms. Hellen de Kloet, Pharmachemie U.S.A. Inc.
CU International, Pharmachemie B.V.

RECORD OF TELEPHONE CONVERSATION

Date: 2-10-1998
Product Name: Megestrol Acetate Tablets
ANDA Number: 74-745
FIRM Name: **Pharmachemie BV**

Name and Title
of Person with
Whom Conversation
Was Held: Mrs. Helen deKloet.

Participant tel.#: 508 393-0973

Minutes of Conversation:

We called *Pharmachemie* regarding a point not clear in the telephone amendment of Feb. 5, 1998.

We had previously asked *Pharmachemie* to please update the API specs to USP Supplement 5 regarding In the amendment they just changed the name of to We therefore asked them today to please revise the API specifications to include both not covered under (as this covers

Ms. deKloet said she would get back to us before the end of this week.

The firm then should provide a tel. amendment, so titled, and fax a copy to RWT as stated earlier followed by a hard copy to OGD as usual.

NAMES of OGD Representatives
with SIGNATURES:

Michael Smela
Robert W. Trimme

Division of Chemistry I, Branch II (HFD-625)

file X:\new\firmsnz\Pharmachem\telecons\74745t-2.tel

2/10-98

2/10/98

RECORD OF TELEPHONE CONVERSATION

Date: 1-27-1998
Product Name: Megestrol Acetate Tabs
ANDA Number: 74-745
FIRM Name: **Pharmachemie BV**

Name and Title of Person with Whom Conversation Was Held: Bruce Manning in the absence of Ms. Helen deKloet.
A fax (attached) dated Oct. 10, 1996 from Pharmachemie BV stated that Mr. Manning [at New England Biomedical Research in Northborough MA] has been authorized to act on behalf of Pharmachemie with the FDA.

Participant tel.#: 508 393-0973

Minutes of Conversation:

We called Pharmachemie regarding 3 points not clear in the application.

1. To please update the API specs to USP Supplement 5 re
2. To revise their impurity specifications for release and stability so that it reads (suggested) per individual and total. Currently it reads only
for stability
3. Regarding the They should state that all the production batches, not just the 3 validation batches, be subject to They may at a later date supplement this application to remove

The firm then should provide a tel. amendment, so titled, and fax a copy to RWT followed by a hard copy to OGD as usual.

NAMES of OGD Representatives with SIGNATURES:

Michael Smela
Robert W. Trimmer *u* *1-28-98*

Division of Chemistry I, Branch II (HFD-625)

file X:\new\firmnsnz\Pharmachem\74745t-1.tel

TELEFAX TRANSMISSION

To: Mike Smela
Office of Generic Drugs
Food and Drug Administration

Fax: 301-594-0180

CC: Dr. Nykerk (Pharmachemie, BV)
Ms. deKloet

¹⁴⁷¹⁹²
31-23-5-312879
393-0974

From: Bruce R. Manning
New England Biomedical Research, Inc.
P.O. Box 809, 27 South Street
Northborough, MA 01532
USA

Fax: (508) 393-3780
Phone: (508) 393-3100
Email: bmanning@nebr.tiac.net

Date: January 27, 1998

Pages: 2

Dear Mr. Smela:

Thank you for your telephone call today concerning questions related to a pending Pharmachemie application. Attached is a copy of an authorization from Pharmachemie, B.V. which authorizes me to act on their behalf in connection with FDA communications.

Please feel free to contact me in Ms. deKloet's absence concerning your questions on their pending application.

Best regards,



Bruce R. Manning

BRM/mcf



PHARMACHEMIE BV

Svensweg 5, Haren
1701 BX Haren
The Netherlands
Phone +31 23 5 147 147
Fax +31 23 5 312 870
telex 411721 phchem nl
AON AMRO Bank
No. 48 62 11 401
No. 56 01 14 885
Postbank no. 1A 89 85

Mr. D. Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Date : October 10th, 1996
Ref. : mw.682.96

Subject: Authorization

Dear Mr. Sporn,

Pharmachemie B.V. has retained Mr. Bruce R. Manning of New England Biomedical Research, Inc. as a consultant in regulatory matters to represent Pharmachemie B.V..

Mr. Manning has been authorized to act on behalf of Pharmachemie B.V. in communications with the U.S. Food and Drug Administration (FDA).

Sincerely yours,
PHARMACHEMIE B.V.

A.J. Nykerk
Senior Vice President
Product Development

NOV 10 1997

MINOR AMENDMENT

ANDA 74-745



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Pharmachemie USA, Inc.

PHONE: (508) 393-0973

ATTN: Hellen de Kloet

FAX: (508) 393-0974

FROM: Sheila O'Keefe

PROJECT MANAGER (301) 827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 13, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Megestrol Acetate Tablets USP, 40 mg.

Reference is also made to your amendment(s) dated July 1, 1996, and March 14 and April 10, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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NOV 10 1997

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 74-745
Drug Product:

Applicant: Pharmachemie USA, Inc.
Megestrol Acetate Tablets USP, 40 mg.

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

1. Regarding your response to our last deficiency letter concerning individual which includes specifications for and average test results please provide a
2. Please be advised that Drug Master File for the active ingredient is still deficient. The holder of the DMF has been notified.
3. We note that you have updated and incorporated the USP 23, Supplement 5, dissolution testing (75 rpm) as specified. Please provide data for your biobatch using the revised dissolution specifications, per USP 23 Apparatus 2 (paddle) at 75 rpms. Please commit to current USP testing for both release and stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.
2. Since the subjection drug product is an official article in the USP, the approval to use an analytical procedure that differs from that in the USP does not release the applicant from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be consider conclusive.
3. Please provide any additional available long term stability data for this product.
4. Your response must also address the labeling deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-745

Pharmachemie B.V.
Attention: Hellen de Kloet
323 Davis Street
Northborough, MA 01532

SEP 16 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated September 13, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Megestrol Acetate Tablets USP, 40 mg.

Reference is made to our not approvable fax of November 10, 1997.

The following comments pertain to labeling deficiencies only.

In addition to the comments regarding your insert labeling in our letter of November 10, 1997, revise your insert labeling to be in accord with recent changes in the labeling of the listed drug Megace® (Bristol-Myers Squibb Company; Approved September 4, 1997; Revised July 1996) as follows:

1. CONTRAINDICATIONS

Revise this subsection to read as follows:

History of hypersensitivity to megestrol acetate or any component of the formulation. Megestrol acetate tablets are contraindicated as a diagnostic test for pregnancy.

2. WARNINGS

Insert the following text as the last paragraph:

Although the glucocorticoid activity of megestrol acetate has not been fully evaluated, laboratory evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in association with megestrol. Rare cases of clinically apparent adrenal suppression should be considered in any patient

taking or withdrawing from chronic megestrol therapy who presents with symptoms of adrenal insufficiency such as hypotension, nausea, vomiting, dizziness, or weakness. Laboratory evaluation for adrenal insufficiency and replacement stress doses of a rapidly acting glucocorticoid may be indicated for such patients.

3. PRECAUTIONS

a. General - Revise to read as follows:

...cancer. Use with caution in patients with a history of thromboembolic disease.

b. Insert the following subsection following "General":

Use in Diabetics: Exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of megestrol.

c. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise to read as follows:

Administration of megestrol acetate to female dogs for up to 7 years is associated with an increased incidence... (see WARNINGS section).

4. ADVERSE REACTIONS

a. Thromboembolic Phenomena - ...embolism (in some cases fatal) have been reported.

b. Glucocorticoid Effects - Revise this subsection to read as follows:

(see WARNINGS and PRECAUTIONS sections).

c. Other Adverse Reactions - Revise to read as follows:

Heart failure, nausea...breakthrough menstrual bleeding, ...hyperglycemia, glucose intolerance, alopecia...syndrome, mood changes, hot flashes, sweating and rain.

Please revise your package insert labeling, and submit in final print with your amendment to our November 10, 1997 letter. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

This letter addressed unique issues involving only labeling. Again, we refer you to our letter of November 10, 1997, for the requirements to reopen the file on this application.

Sincerely yours,

 1/12-15-97
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-745
Dup/Division File
HFD-600/Reading File
X:\NEW\FIRMSNZ\PHARMACH\LTRS&REV\74745.LOL
Letter Out

Endorsements:

HFD-613/CHolquist C. Holquist 12/12/97
HFD-613/JGrace

323 Davis Street
Northborough
Massachusetts 01532
Telephone: (508) 393-0973
Fax: (508) 393-0974
email: pchusa@gls.net

PHARMACHEMIE U.S.A., INC.



teletax message

To : Office of Generic Drugs/CDER/FDA
Attn : Dr B. Trimmer
Faxnumber : 301 594 0180
From : Hellen de Kloet
Date : February 12, 1998
Subject : **Megestrol Acetate Tablets, USP 40 mg ANDA 74-745**
Amendment on Telephone Amendment #5
Cc : -
Number of pages : 3 (Including this page)

Dear Mr. Trimmer,

This morning we discovered a slight mistake in Telephone Amendment #5 submitted to you by fax yesterday. On page 19 of the amendment the standard solution mentioned the impurities the other impurities, as stated in the specifications were not mentioned at all.

This minor error has been amended. Please find hereafter the revised page 19 and 19*1 of Telephone Amendment #5.

The revised pages are included in the hard copies which will be send to you by mail.

We apologize for the inconvenience.

Sincerely yours,

Ms Hellen de Kloet
Vice President
Medical & Regulatory Affairs