CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040194

Trade Name : METHYLPREDNISOLONE TABLETS USP

Generic Name: Methylprednisolone Tablets USP 4mg

Sponsor : Invamed, Inc.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040194

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040194

APPROVAL LETTER

ANDA 40-194

OCT 31 1997

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Rt. 130 North
Dayton, NJ 08810

Dear Dr. Patel:

This is in reference to your abbreviated new drug application dated June 18, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylprednisolone Tablets USP, 4 mg.

Reference is also made to your amendments dated February 28, September 11, and October 21, 1997.

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 that your Methylprednisolone Tablets USP, 4 mg are bioequivalent and, therefore therapeutically equivalent, to the listed drug (Medrol® Tablets 4 mg by Pharmacia and Upjohn Company). 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 FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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 FDA-2253 at the time of their initial use.

Sincerely yours,

/S/ for 10/31/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040194

FINAL PRINTED LABELING

NDC 52189-351-21 NSN 6505-01-131-5619

invamed inc.

Methylprednisolone Tablets, USP

4 mg

Unit of Use 21 Tablets

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

EACH TABLET CONTAINS:
Methylprednisolone ..... 4 mg

DIRECTIONS FOR USE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all drugs out of the reach of children.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Lot No.:
Exp. Date:

invamed inc.
Dayton, NJ 08810 USA
MF # 1174

N 3 52189-351-21 4

METHYLPREDNISOLONE TABLETS USP, 4 mg
ANDA # 40-194
MAJOR AMENDMENT
(RESPONSE TO FDA LETTER DATED 01/10/97)

NDC 52189-351-30

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone ..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all the drugs out of the reach of the children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-30 6

Lot No.:
Exp. Date:
MF # 1042

NDC 52189-351-30

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone ..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all the drugs out of the reach of the children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-30 6

Lot No.:
Exp. Date:
MF # 1042

NDC 52189-351-30

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone ..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

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INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-30 6

Lot No.:
Exp. Date:
MF # 1042

METHYLPREDNISOLONE TABLETS USP, 4 mg
ANDA # 40-194
MAJOR AMENDMENT
(RESPONSE TO FDA LETTER DATED 01/10/97)

Mango

NDC 52189-351-24

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-24 5

Lot No.:
Exp. Date: OCT 31 19[illegible]
MF # 1040

NDC 52189-351-24

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-24 5

Lot No.:
Exp. Date: [illegible] 31 [illegible]
MF # 1041

NDC 52189-351-24

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-24 5

Lot No.:
Exp. Date: [illegible] 31
MF # 1041

NDC 52189-351-24

invamed inc.

Methylprednisolone Tablets, USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Methylprednisolone..... 4 mg

USUAL DOSAGE: See accompanying prescribing information.

Keep patient under close observation of a physician.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-24 5

Lot No.:
Exp. Date:
MF # 1041

000260

Dosage Directions **To remove tablet, press from this side.**

1st day

Take 2 tablets before breakfast, 1 tablet after lunch and after supper, and 2 tablets at bedtime.

2nd day

Take 1 tablet before breakfast, 1 tablet after lunch and after supper, and 2 tablets at bedtime.

3rd day

Take 1 tablet before breakfast and 1 tablet after lunch, after supper, and at bedtime.

4th day

Take 1 tablet before breakfast, after lunch, and at bedtime.

5th day

Take 1 tablet before breakfast and at bedtime.

6th day

Take 1 tablet before breakfast.

invamed inc.

Methylprednisolone Tablets, USP

4 mg **Unit of Use**

Unless otherwise directed by your physician, all six (6) tablets in the row labeled 1st day should be taken the day you receive your prescription, even though you may not receive it until late in the day. All six (6) tablets may be taken immediately as a single dose, or may be divided into two or three doses and taken at intervals between the time you receive the medicine and your regular bedtime.

3.465"

4.567"

NDC 52189-351-21 *NSN 6505-01-131-5619*

invamed inc.

Methylprednisolone Tablets, USP

4 mg

Unit of Use 21 Tablets

EACH TABLET CONTAINS:
Methylprednisolone ..... 4 mg

DIRECTIONS FOR USE: See accompanying prescribing information.
Keep patient under close observation of a physician.
Keep this and all drugs out of the reach of children.
CAUTION: Federal law prohibits dispensing without prescription.
Store at controlled room temperature 15° to 30°C (59° to 86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-351-21 4

Lot No.:
Exp. Date:

3.465"

CUSTOMER	
PCI/INVAMED	
GDN 3309501	DATE 2/7/97

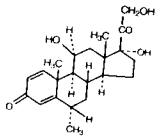
000282

METHYLPREDNISOLONE TABLETS, USP 4 mg

DESCRIPTION

Methylprednisolone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone is a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1, 4-diene-3, 20-dione,11,17,21-trihydroxy-6-methyl-(6α, 11β)- and the molecular weight is 374.48. The structural formula is represented below:



Each tablet, for oral administration, contains 4 mg methylprednisolone. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone tablets are indicated in the following conditions:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoids supplementation is of particular importance).
Congenital adrenal hyperplasia
Hypercalcemia associated with cancer
Nonsuppurative thyroiditis

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Psoriatic arthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
Ankylosing spondylitis
Acute and subacute bursitis
Acute nonspecific tenosynovitis

1. **Endocrine Disorders**
   - Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoids supplementation is of particular importance).
   - Congenital adrenal hyperplasia
   - Hypercalcemia associated with cancer
   - Nonsuppurative thyroiditis
2. **Rheumatic Disorders**
   - As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   - Psoriatic arthritis
   - Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   - Ankylosing spondylitis
   - Acute and subacute bursitis
   - Acute nonspecific tenosynovitis
   - Acute gouty arthritis
   - Post-traumatic osteoarthritis
   - Synovitis of osteoarthritis
   - Epicondylitis
3. **Collagen Diseases**
   - During an exacerbation or as maintenance therapy in selected cases of:
   - Systemic lupus erythematosus
   - Systemic dermatomyositis (polymyositis)
   - Acute rheumatic carditis
4. **Dermatologic Diseases**
   - Pemphigus
   - Bullous dermatitis herpetiformis
   - Severe erythema multiforme (Stevens-Johnson syndrome)
   - Exfoliative dermatitis
   - Mycosis fungoides
   - Severe psoriasis
   - Severe seborrheic dermatitis
5. **Allergic States**
   - Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   - Seasonal or perennial allergic rhinitis
   - Bronchial asthma
   - Contact dermatitis
   - Atopic dermatitis
   - Serum sickness
   - Drug hypersensitivity reactions
6. **Ophthalmic Diseases**
   - Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   - Allergic corneal marginal ulcers
   - Herpes zoster ophthalmicus
   - Anterior segment inflammation
   - Diffuse posterior uveitis and choroiditis
   - Sympathetic ophthalmia
   - Allergic conjunctivitis
   - Keratitis
   - Chorioretinitis
   - Optic neuritis
   - Iritis and iridocyclitis
7. **Respiratory Diseases**
   - Symptomatic sarcoidosis
   - Loeffler's syndrome not manageable by other means
   - Berylliosis
   - Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   - Aspiration pneumonitis
8. **Hematologic Disorders**
   - Idiopathic thrombocytopenic purpura in adults
   - Secondary thrombocytopenia in adults
   - Acquired (autoimmune) hemolytic anemia
   - Erythroblastopenia (RBC anemia)
   - Congenital (erythroid) hypoplastic anemia
9. **Neoplastic Diseases**
   - For palliative management of:
   - Leukemias and lymphomas in adults
   - Acute leukemia of childhood
10. **Edematous States**
    - To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
11. **Gastrointestinal Diseases**
    - To tide the patient over a critical period of the disease in:
    - Ulcerative colitis
    - Regional enteritis
12. **Nervous System**
    - Acute exacerbations of multiple sclerosis
13. **Miscellaneous**
    - Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
    - Trichinosis with necrologic or myocardial involvement

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infections and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids

adults
Acute leukemia of childhood

10. Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

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To tide the patient over a critical period of the disease in:
Ulcerative colitis
Regional enteritis

12. Nervous System

Acute exacerbations of multiple sclerosis

13. Miscellaneous

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Trichinosis with necrologic or myocardial involvement

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infections and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone* or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of methylprednisolone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

* If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

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There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**).

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Information for Patients

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

Sodium retention
Fluid retention
Congestive heart failure in susceptible patients
Potassium loss
Hypokalemic alkalosis
Hypertension

Musculoskeletal

Muscle weakness
Steroid myopathy
Loss of muscle mass
Osteoporosis
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage

Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatologic

Impaired wound healing
Petechiae and ecchymoses
Increased sweating
May suppress reactions to skin tests
Thin fragile skin
Facial erythema

Metabolic

Negative nitrogen balance due to protein catabolism

Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache

Endocrine

Menstrual irregularities
Development of Cushingoid state
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Suppression of growth in children
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

The following additional reactions have been reported following oral as well as parenteral therapy:

Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of methylprednisolone may vary from 4 mg to 48 mg per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of methylprednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis

In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Alternate Day Therapy

Alternate Day Therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for re-establishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts

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A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring aoout midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for 1 1/4 to 1 1/2 days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate day therapy should not encourage the indiscriminate use of steroids.
2) Alternate day therapy is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.
3) In less severe disease processes

of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for 1 1/4 to 1 1/2 days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate day therapy should not encourage the indiscriminate use of steroids.

2) Alternate day therapy is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.

3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with alternate day therapy. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended.

   Once control has been established, two courses are available: (a) change to alternate day therapy and then gradually reduce the amount of corticoid given every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

4) Because of the advantages of alternate day therapy, it may be desirable to try patients on this form of therapy who have been on daily corticoid for long periods of time (e.g., patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on alternate day therapy may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (e.g., dexamethasone and betamethasone).

6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

7) In using alternate day therapy it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of alternate-day therapy will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be re-instituted.

9) Although many of the undesirable features of corticosteroid therapy can be minimized by alternate day therapy, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets, USP 4 mg are white, oval-shaped, uncoated, engraved INV above 351 on one side and quadrisect on the other side are supplied as follows:

NDC 52189-351-21 in Unit of Use pack of 21 tablets

NDC 52189-351-24 in bottles of 100 tablets

NDC 52189-351-30 in bottles of 1000 tablets

Store at controlled room temperature 15°C-30°C (59°F-86°F).

of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be re-instituted.

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NDC 52189-351-30 in bottles of 1000 tablets

Store at controlled room temperature 15°C-30°C (59°F-86°F).

Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
INVAMED INC
Dayton, NJ 08810 USA

Date of Revision: September 1997
[L-1147; MF#1044C]

0 114735 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040194

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3 (three)

2. ANDA # 40-194

3. NAME AND ADDRESS OF APPLICANT

Invamed Inc.
Attention: Mahendra Patel
2400 Rt. 130 North
Dayton, NJ 08810

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Methylprednisolone

13. DOSAGE FORM

Tablets

14. STRENGTH

4 mg

10. PHARMACOLOGICAL CATEGORY

Glucocorticoid

11. Rx or OTC

Rx

4. LEGAL BASIS FOR SUBMISSION

There is no exclusivity, and the patent has expired. The RLD is Medrol Tablets USP 4 mg, manufactured by Pharmacia and Upjohn, NDA 11-153.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

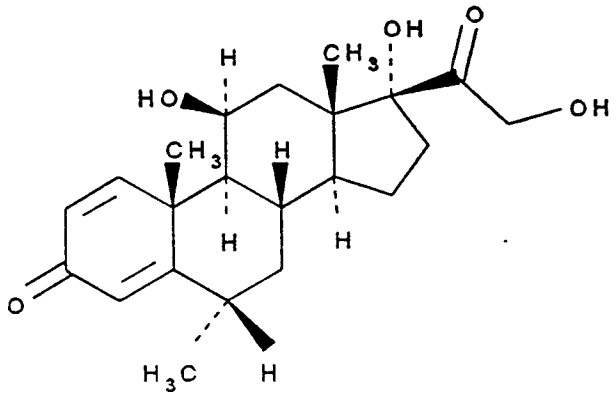
06/18/96 Original ANDA.
09/16/96 Gratuitous amendment to provide for the unit dose pack of 21 count as an additional container/ closure system.
02/28/97 Major Amendment
04/08/97 Letter (new information submitted)
09/11/97 Facsimile amendment
10/21/97 Telephone amendment

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Methylprednisolone USP

$C_{22}H_{30}O_5$; M.W. = 374.48



11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.
CAS [83-43-2]

16. RECORDS AND REPORTS N/A

17. COMMENTS

ANDA 40-194 is **approvable.**

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 40-194 is **approvable.**

19. REVIEWER: DATE COMPLETED:

Liang-Lii Huang, Ph.D. September 24, 1997

cc: ANDA #40-194
ANDA #40-194/Division File
Field Copy
Endorsements:
HFD-627/Liang-Lii Huang, Ph.D./9/24/97
HFD-627/P.Schwartz, Ph.D./9/24/97
X:\NEW\FIRMSAM\INVAMED\LTRS&REV\40194S00.RV3
F/T/gp/September 24, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040194

BIOEQUIVALENCE REVIEW(S)

Div

ANDA 40-194

JAN - 6 1997 ~~1997~~

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Rt. 130
Dayton NJ 08810

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Tablets USP, 4 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 2 1997

DiV

Methylprednisolone
4 mg Tablet
ANDA #40-194
Reviewer: Kuldeep R. Dhariwal
File name: 40194SD.696

Invamed Inc.
2400 Rt. 130
Dayton, NJ 08810
Submission Date:
June 18, 1996

Review of Fasting Bioequivalence Study and Dissolution Data

The firm has submitted a single-dose bioequivalence study under fasting conditions and dissolution data comparing its Methylprednisolone tablet, 4 mg with The Upjohn Company's Medrol®, 4 mg tablet.

Introduction:

Methylprednisolone is a pregna-1,4-diene-3, 20-dione,11, 17, 21-trihydroxy-6-methyl-,(6α, 11β). It is a synthetic glucocorticoid, used primarily as antiinflammatory or immunosuppressant agent. It is indicated in endocrine and rheumatic disorders, collagen and dermatological diseases, allergic states, ophthalmic and respiratory diseases, hematological disorders, neoplastic diseases, edematous states, gastrointestinal diseases and multiple sclerosis, tuberculosis, meningitis and trichinosis. It is readily absorbed from gastrointestinal tract with peak plasma levels occurring at 1-2 hours. The plasma half-life is about 3-4 hours.

The reference listed drug is Medrol® manufactured by The Upjohn Company. It is available in six strengths: 2 mg, 4 mg, 8 mg, 16 mg, 24 mg, and 32 mg.

Bioavailability of Methylprednisolone Tablet, 4 mg under Fasting Conditions:

A. Objective: The objective of this study is to compare the relative bioavailability of methylprednisolone 4 mg tablets (Invamed) with that of Medrol® 4 mg tablets (The Upjohn Company) in healthy adult male subjects under fasting conditions.

B. Study Sites and Investigators:

Clinical Site: [redacted]
Analytical Site: [redacted]
Clinical Investig[redacted]
Medical Investiga[redacted]
Analytical Invest[redacted]
Statistical Analy[redacted]

(b)4 - Confidential Business

Protocol #P95-436: A relative bioavailability study of methylprednisolone 4 mg tablets under fasting conditions" was approved by the IRB of [redacted]

(b)4 - Confidential

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 633, vol.1.2
Study Dates: Period I January 21-22, 1996
Period II January 28-29, 1996
Analysis Dates: Feb. 28 to May 20, 1996

C. Study Design:

The study was designed as a two-way, single-dose, open-label, randomized, two-period, two-treatment, two-sequence crossover study with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 10 hours prior to dosing until at least 18 hours after dosing. The subjects were assigned as follows:

Sequence	Subject number	Phase I	Phase II
1	1,5,7,9,10,12,13,14,16,20,21,22,25	A	B
2	2,3,4,6,8,11,15,17,18,19,23,24,26	B	A

A = Methylprednisolone Tablets 4x4 mg; Invamed, Inc., Lot #D951204, Batch size [redacted](b)4 - [redacted]tablets; Manufacture Date: Dec. 1995; Assay: 97.1%; Content Uniformity: 99.5%

B = Medrol® Tablets, 4x4 mg; The Upjohn Company; Lot # 244MJ, Expiry Date: 8/99; Assay: 98.0%; Content Uniformity: 98.7%

Formulation of the test product is shown in Table 7.

The subjects fasted for 10 hours prior to dosing and until at least 4 hours after dosing. Fluids were not allowed from 1 hour prior to dose administration until 2 hours after dosing. At 2

hours post-dose, all subjects consumed 240 mL of water. Identical meals were served during each confinement period. The subjects were not permitted to lie down or sleep for the first 4 hours after dose administration. Blood pressure and heart rate were measured prior to dosing and at 18 hours after dose.

D. Subject Selection:

Twenty-six healthy male volunteers entered the study and all twenty-six completed the study. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age, weight range within ±10% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table
- good health as determined by medical histories and physical examinations done within 21 days prior to initiation of the study. Blood chemistry, hematology, and urine analysis values within clinically acceptable limits

Subjects were excluded from this study based on the following criteria:

- recent history of drug or alcohol addiction or abuse
- presence of clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, endocrine, or neurologic system(s) or psychiatric disease
- positive hepatitis B surface antigen, HIV test
- history of allergic response to methylprednisolone or related drugs
- history of clinically significant illness during the 4 weeks prior to period I dosing
- history of clinically significant allergies including drug allergies
- current use of tobacco products
- use of any drug known to induce or inhibit hepatic drug metabolism in 30 days prior to period I dosing
- blood donation greater than 150 mL within 30 days prior to period I dosing
- plasma donation within 14 days prior to period I dosing
- participation in clinical study using investigational drug within 30 days prior to period I dosing

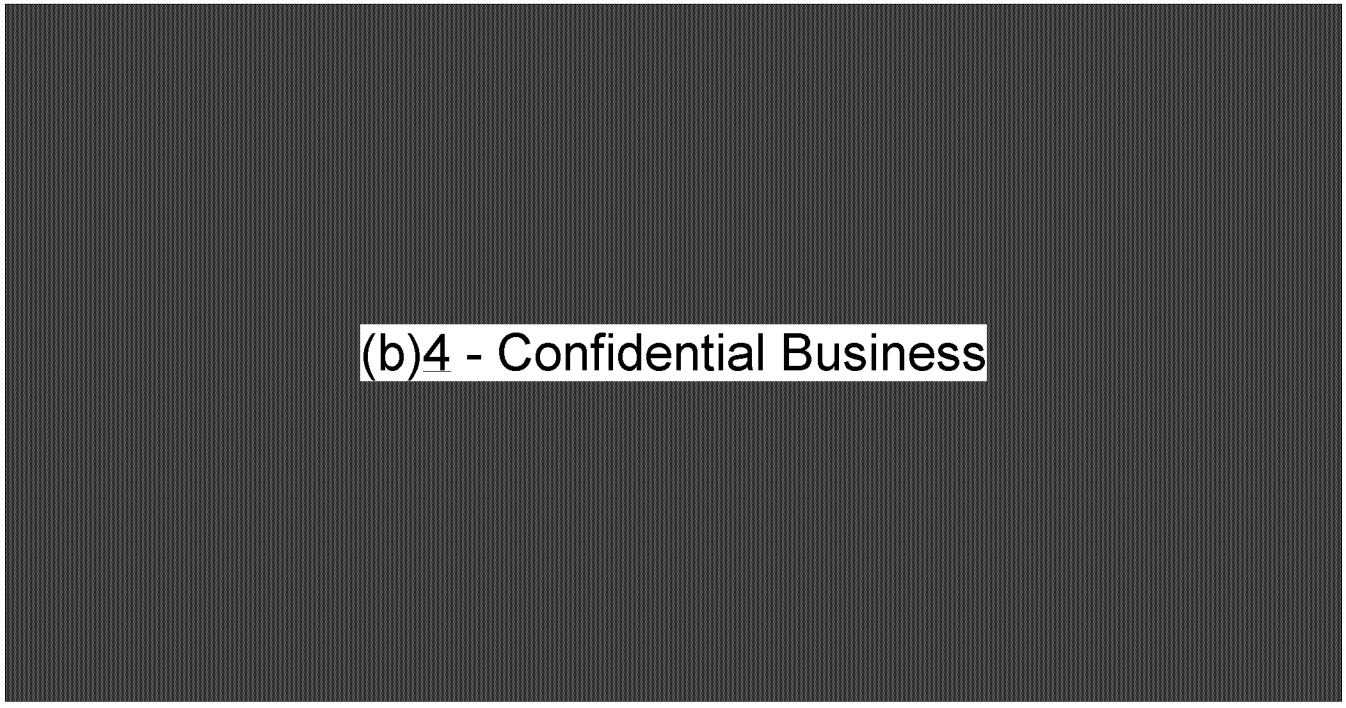
Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medication within 7 days of the period I dosing
- no alcohol and caffeine containing foods or beverages at least 48 hours prior to days on which dosing was scheduled and during the periods when the blood samples were collected
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood was collected in EDTA vacutainers within one hour prior to dosing (0 hour) and after dose administration at 20, 40, and 60 minutes and 1.5,2,2.5,3,4,5,6,8, 10,12,14,16, and 18 hours during each study period. The samples remained at the blood collection station until all samples had been collected for that collection period. The vacutainer samples were then transferred to the processing laboratory. The blood was centrifuged at 2400 rpm for 15 minutes at 4°C and the plasma separated. The plasma samples were immediately placed in a freezer at -20°C or colder. The samples were shipped to the analytical facility on dry ice.

F. Analytical Methods:



G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration [C(T)]. AUC_{0-inf} was calculated by adding the value of C(T)/KE to AUC_{0-t} where KE is the elimination rate constant. The KE was obtained from slope of the line, fitted by linear least squares regression, through the terminal points of the log(base e) of the concentration. Half-life, T_{max}, and C_{max} were also calculated. Statistical analyses were performed using SAS® software. The study power calculations and 90% confidence intervals calculations were based on the least-squares means generated by the SAS LSMEANS option to the SAS GLM procedure and the standard error of the estimate as given by the GLM procedure.

H. Results:

1. Clinical:

All twenty-six subjects who entered the study, completed the study. The plasma samples from all subjects were analyzed. Each subject completed the study exit procedures within 14 days after the last blood sample collection. The exit procedures included general observations, a physical examination, blood pressure, heart rate, and temperature evaluation.

Adverse Events:

Following 9 subjects experienced adverse events during the study. None of the events were considered serious.

Subject #	Phase	Product	Sign/Symptom
2	I	Ref	Headache
4	I	Ref	Bottom wisdom teeth pain, headache
9	II	Ref	Headache
11	II	Test	Headache
16	I	Test	Sore throat
17	I	Ref	Upset stomach
	II	Test	Headache

20	I	Test	Sore throat
	II	Ref	Headache
21	I	Test	Hematoma, nausea, pale
24	I	Ref	Headache, subject took Tylenol

In general, all subjects had a higher WBC at study exit compared to the prestudy screening. An increase in the number of leukocytes in the blood is a pharmacological effect associated with the glucocorticoids. For those subjects who required a repeat WBC at study exit, the repeat results were within the reference range. Nine subjects had clinical chemistry values outside the reference range at exit, however they were not considered clinically significant and hence were not repeated.

Deviations in the study:

1. There were three deviations from the protocol requirement of no OTC medications within 7 days of period I dosing. Subject #12 took one tablet of multivitamin 6 days before the study. Subject #21 took acetaminophen and Nyquil for fever, cough, and headache on 3,4, and 5 days before start of the study.

2. Following deviations in scheduled phlebotomy times were reported:

Subject #	Period	Sampling Time	Deviation
4	II	10:00	2 minutes late
21	I	10:00	2 minutes late
23	I	2:30	2 minutes late

Actual blood collection times were used in PK calculations.

Reassays: There were 884 samples to be analyzed in this study.
a) All samples from subject numbers 3,4,9, and 10 were repeated because QC samples did not meet the acceptance criteria during the first run.
b) All samples from subjects 21 and 22 (run 11) were repeated because of late eluting matrix peaks interfering with the chromatograms (page 387, vol.1.1). However on page 390, it is stated that the analysis was repeated "due to most of the samples and controls being below scale".

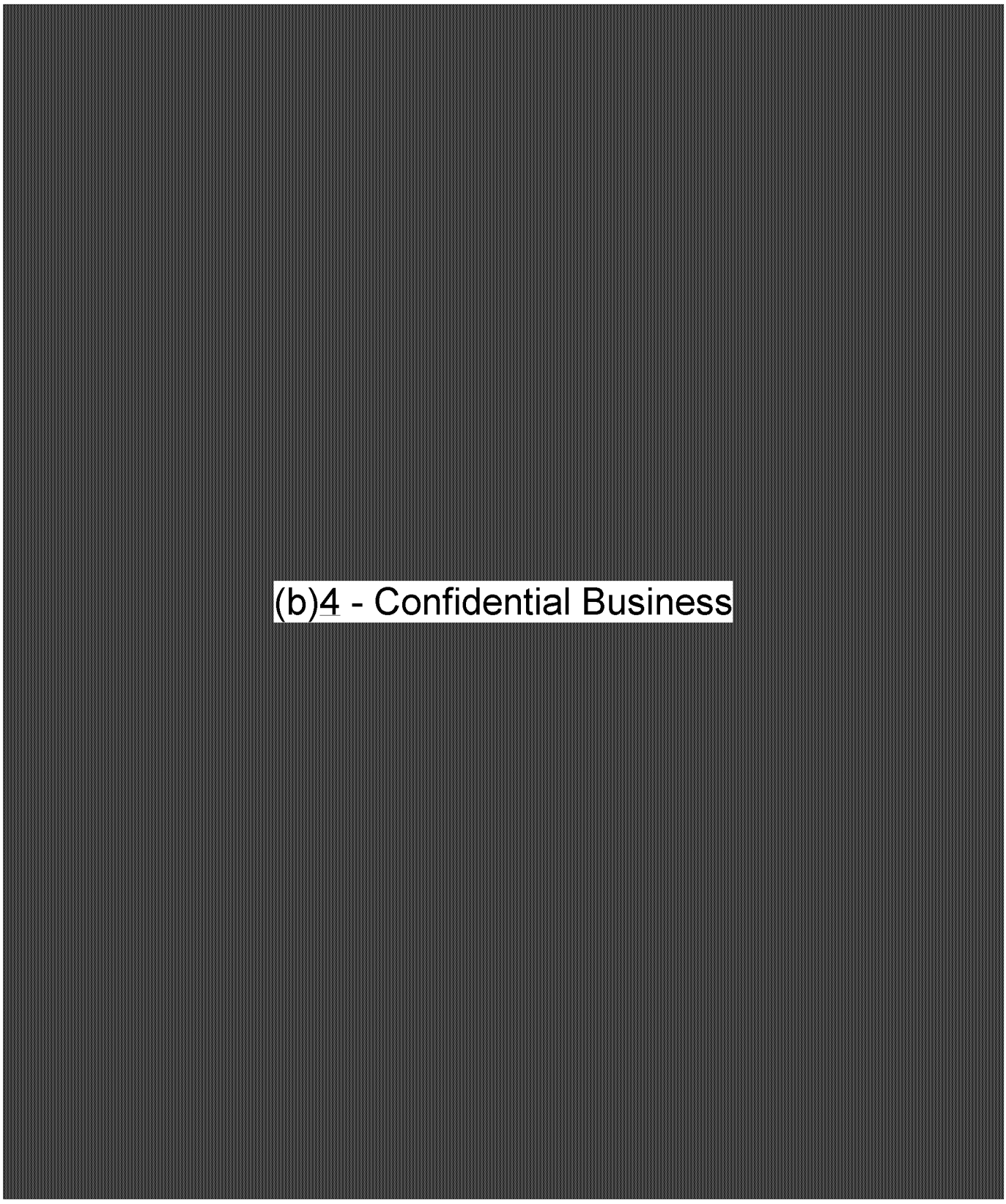
c) Run #14 comprising of 55 repeat assays was rejected because of column resolution. The samples were reassayed using a new column and repeated values are reported.
d) In addition, following 90 samples were reassayed for the reasons shown against them:

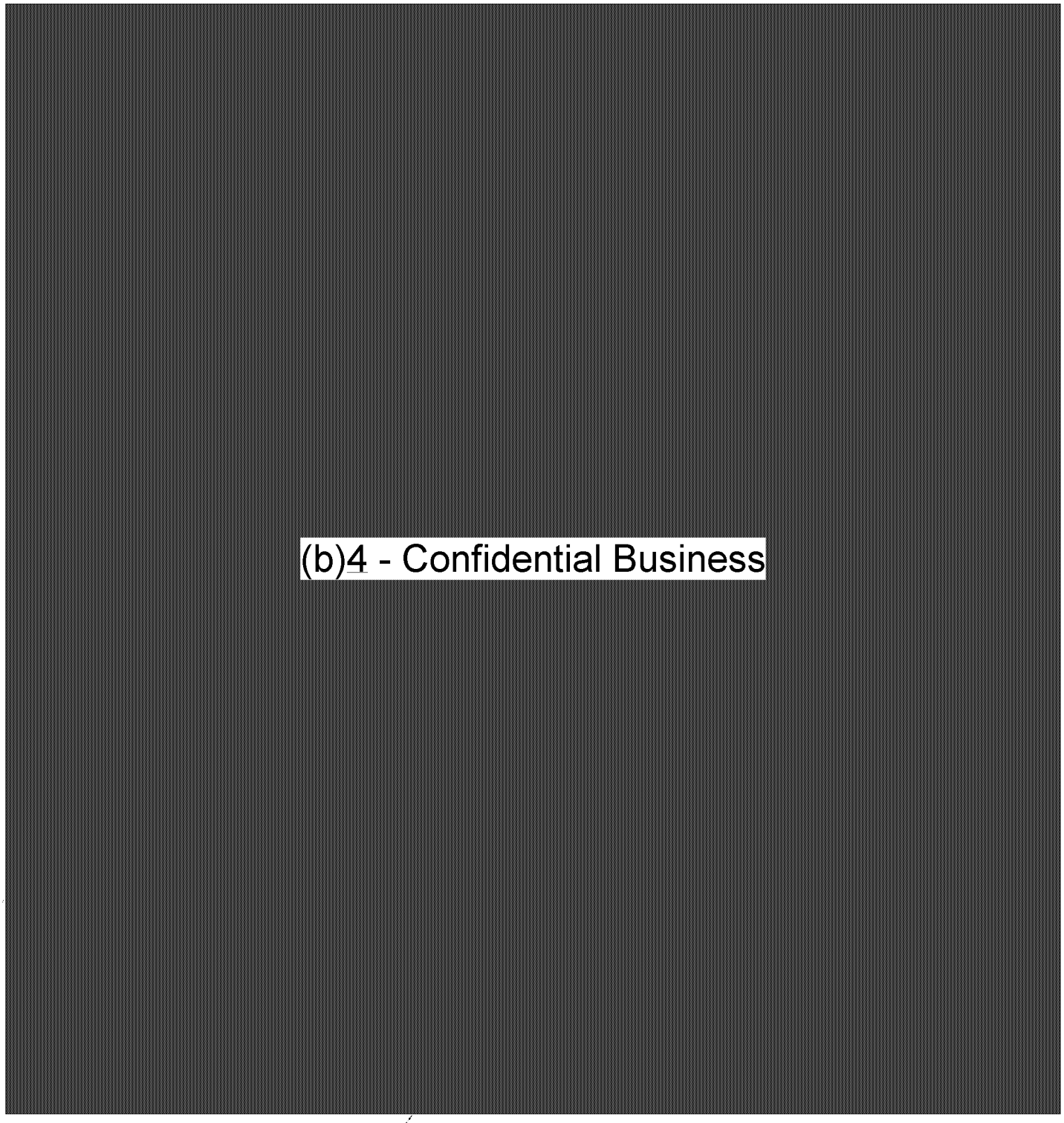
# of samples	Reason for reassay
18	peak in 0 hour samples
45	anomalous value
7	chromatographic interference
2	autoinjector malfunction
1	laboratory accident
2	low internal standard
12	integrator malfunction
1	repeated by mistake
1	low injection
1	poor chromatography

Eighteen pre-dose (0 hour) samples were repeated because they showed a matrix peak eluting at or close to the retention time of the drug peak. Ten of these predose samples showed no detectable drug concentration on repeat analysis. However, mean of original and repeat value was taken and reported if it was higher than LLOQ. For the other eight pre-dose samples, there was not enough sample remaining to repeat the analysis and therefore the original value was reported.

2. Analytical:

(b)4 - Confidential Business


(b)4 - Confidential Business


(b)4 - Confidential Business

3. Pharmacokinetics/Statistics:

All twenty-six subjects recruited for the study, completed the study. The plasma samples from all subjects were assayed for methylprednisolone. Nine subjects had chromatograms with interfering peaks which resulted in measurable levels of methylprednisolone in the predose (0 hour) samples. The firm has submitted the clinical and statistical data with and without these nine subjects. The mean plasma concentrations of methylprednisolone at each time point after test and reference products are shown in Tables 1 and 2. The time courses of methylprednisolone concentration after the two products are shown in Figures 1, 2 (data from all subjects) and Figures 3 and 4 (data from subjects without 0 hour levels). There is no significant difference in mean plasma concentrations at any time point. The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Methylprednisolone (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
1	437.47	446.12	437	446
11	313.86	321.66	314	322
20	494.44	509.22	494	509

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 5. The test/reference ratio for AUC_{0-t} ranged from 0.71 to 1.454 (mean 1.01), AUC_{0-inf} ranged from 0.72-1.43 (mean 1.00), and C_{max} ranged from 0.83-1.32 with a mean of 1.02.

Table 6 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.92-0.99 for test and 0.90-0.99 for reference product.

Pharmacokinetic results using data from all subjects:

The AUC_{0-t} and AUC_{0-inf} were both 2% lower in test product compared to reference product. The C_{max} of the test and reference products

was same, however it occurred about 13 minutes later in test product (Tables 1 and 3). Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	95.1-104%	95.12-103.71%
$LNAUC_{0-inf}$	94.9-103%	94.92-103.13%
LNC_{max}	98.0-106%	97.97-106.10%

Statistical analysis of data show significant period effects for untransformed as well as log transformed AUC_{0-t} and AUC_{0-inf}.

Pharmacokinetic results excluding data from subjects with 0 hour levels:

The AUC_{0-t} and AUC_{0-inf} of the test product were 2% higher than the reference product. The C_{max} of the test product was 4% higher and occurred about 23 minutes later than the reference product (Tables 2 and 4). Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	96.8-107%	96.76-107.39%
$LNAUC_{0-inf}$	97.3-107%	97.38-107.43%
LNC_{max}	99.9-109%	99.87-109.20%

The 90% confidence intervals remain within acceptable limits of 80-125% after eliminating data from subjects who had detectable methylprednisolone levels at 0 hour due to interfering peaks. Statistical analysis of data show significant period effect for untransformed and log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}.

In Vitro Dissolution Testing:

The dissolution testing was done using apparatus II (paddle) at 50 rpm and 900 mL of deionized water as medium. The drug products used in the dissolution tests were from the same lot used in the bioequivalence studies. The dissolution profiles of the test and reference products are almost similar (Table 8). The test product dissolves greater than (b)4 in 30 minutes.

Comments:

1. All twenty-six subjects recruited for the study, completed the study. The plasma samples from all subjects were assayed for methylprednisolone. Nine subjects experienced adverse events during the study. None of the events were considered serious. In general, all subjects had a higher WBC count at study exit compared to the screening time. An increase in the number of leukocytes in the blood is a pharmacological effect associated with the glucocorticoids.

2. A large number of samples were repeated in this study. All samples from subject numbers 3,4,9,10,21, and 22 were repeated. Run number 14 (repeats I) comprising of 55 samples was repeated. Additionally, 90 samples from various subjects were repeated due to reasons given above (see reassays). The firm has provided two sets of statistical data. The first set includes data from all subjects (n=26) and the second set excludes subject numbers 3,4,9,10,21, 22,23,25, and 26 (n=17) who had detectable levels of methylprednisolone at 0 hour due to interfering peaks. Most of the repeat analysis was done on samples from the subjects which are excluded in the second set of data analysis. The study meets the bioequivalence criteria using data from all subjects as well as using data from 17 subjects. Some subjects showed drug levels at 0 time in the first or second period, however these subjects had $T_{½}$ about or below 5 hours. Thus, suggesting that 0 hr drug levels are due to chromatographic interference as stated by the firm and not due to incomplete washout period (one week).

3. Results using data from all subjects:
The AUC_{0-t} and AUC_{0-inf} were both 2% lower in test product compared to reference product. The C_{max} of the test and reference products was same, however it occurred about 13 minutes later in test

product. Statistical analysis of data show significant period effects for untransformed as well as log transformed AUC_{0-t} and AUC_{0-inf}. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%.

Results excluding data from subjects with 0 hour levels:
The AUC_{0-t} and AUC_{0-inf} of the test product were 2% higher than the reference product. The C_{max} of the test product was 4% higher and occurred about 23 minutes later. Statistical analysis of data show significant period effect for untransformed and log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%.

4. The study results demonstrate that test product is bioequivalent to reference product.

5. The dissolution testing was done using USP specifications. The firm has demonstrated that greater than (b)4 of the test product is dissolved in 30 minutes. The *in vitro* dissolution data are acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Invamed Inc., on its methylprednisolone tablet 4 mg, lot #D951204, comparing it to the reference product Medrol® tablet 4 mg, lot #244MJ manufactured by The Upjohn Company has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Invamed's methylprednisolone 4 mg tablet is bioequivalent to the reference product Medrol® 4 mg tablet manufactured by The Upjohn Company.

2. The dissolution testing data on the test product are acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37°C using apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of methylprednisolone in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

/S/ 12/13/96

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 12/17/1996

/S/

Concur: _____ Date 1/2/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #40194 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 090596; Final: 121396

Table 1

Methylprednisolone Plasma Concentrations (ng/mL), Data from All Subjects Including 0 Hour Levels: Arithmetic Means ± Standard Deviation (n=26)

Time (h)	Test	Reference	Test/Ref
0	1.045±2.473*	1.857±2.964**	0.56
0.33	11.946±12.863	16.824±14.418	0.71
0.67	50.057±32.773	54.527±33.526	0.92
1.00	73.027±34.676	81.719±40.688	0.89
1.50	92.212±28.543	91.615±36.301	1.00
2.00	99.462±26.988	96.908±29.223	1.03
2.50	94.823±23.020	94.996±24.459	1.00
3.00	88.019±22.780	88.927±24.450	0.99
4.00	67.192±21.001	70.135±24.012	0.96
5.00	51.577±17.170	51.300±17.725	1.00
6.00	36.720±13.366**	37.477±14.387	0.98
8.00	18.910±7.411	18.832±8.078	1.00
10.0	9.614±4.764	10.138±5.647	0.95
12.0	5.560±3.887**	4.680±3.849	1.19
14.0	3.325±3.732	3.010±3.600	1.10
16.0	1.052±2.118	1.251±2.355	0.84
18.0	1.091±1.882	1.156±3.240	0.94
Parameter			
AUC_{0-t} (ng/mLxh)	509.457±144.9	517.388±165.57	0.98
AUC_{0-inf} (ng/mLxh)	526.628±146.7	532.793±171.36**	0.99
C_{max} (ng/mL)	110.323±24.32	109.565±30.562	1.00
T_{max} (h)	2.077±0.542	1.865±0.715	1.11
Half-life (h)	2.680±1.155	2.475±0.92**	1.08
Elim. rate constant (h^{-1})	0.292±0.088	0.308±0.086	0.95

* n=24

** n=25

Table 2

Methylprednisolone Plasma Concentrations (ng/mL): Data From Subjects Without 0 Hour Levels: Arithmetic Means ± Standard Deviation (N=17)

Time h	Test	Reference	Test/Ref
0	0	0	-
0.33	8.086±7.57	15.498±13.70	0.52
0.67	43.611±24.65	53.324±30.99	0.82
1.00	67.424±31.67	82.776±36.10	0.81
1.50	86.859±25.41	90.288±29.45	0.96
2.00	96.482±25.58	94.324±23.26	1.02
2.50	93.041±22.00	89.753±19.82	1.04
3.00	86.065±20.25	82.000±20.19	1.05
4.00	64.818±19.02	62.153±18.43	1.04
5.00	50.806±15.68	46.506±14.06	1.09
6.00	35.471±12.71	33.559±13.40	1.06
8.00	17.975±6.78	16.384±6.791	1.10
10.0	8.682±3.905	8.164±4.457	1.06
12.0	4.668±3.282	3.341±3.336	1.40
14.0	1.830±2.84	1.966±2.860	0.93
16.0	0.238±0.98	0.588±1.313	0.40
18.0	0.392±1.11	0.00	
Parameter			
AUC_{0-t} (ng/mLxh)	479.947±123.62	471.800±135.8	1.02
AUC_{0-inf} (ng/mLxh)	494.113±124.621	484.183±136.5	1.02
C_{max} (ng/mL)	107.141±22.486	102.765±23.69	1.04
T_{max} (h)	2.147±0.523	1.765±0.687	1.22
Half-life(h)	2.195±0.472	2.106±0.362	1.04
Elim. rate constant (h^{-1})	0.328±0.063	0.339±0.064	0.97

Table 3

Methylprednisolone Plasma Concentrations (n=26), Data From All Subjects Including 0 Hour Levels
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	509.46±10.1	517.38±10.1	0.98	93.7-103%
AUC_{0-inf} (ng/mLxh)	526.62±9.91	537.06±10.3	0.98	93.5-103%
C_{max} (ng/mL)	110.32±1.93	109.56±1.93	1.00	96.4-105%
T_{max} (h)	2.077±0.105	1.865±0.105	1.11	97.7-125%
Half-life(h)	2.680±0.115	2.522±0.119	1.06	95-118%
Elim. rate constant (h^{-1})	0.292±0.009	0.303±0.010	0.96	88.6-104%
$LNAUC_{0-t}$	6.1930±0.018	6.1995±0.018	1.00	95.1-104%
$LNAUC_{0-inf}$	6.228±0.017	6.2387±0.017	1.00	94.9-103%
LNC_{max}	4.680±0.016	4.660±0.016	1.00	98.0-106%

Table 4

Methylprednisolone Plasma Concentrations (n=17): Data From Subjects Without 0 Hour Levels
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (ng/mLxh)	479.30±12.16	474.39±12.16	1.01	94.7-107%
AUC_{0-inf} (ng/mLxh)	493.49±11.86	486.71±11.86	1.01	95.3-107%
C_{max} (ng/mL)	107.18±1.88	103.17±1.88	1.04	99.4-108%
T_{max} (h)	2.145±0.106	1.774±0.106	1.21	106-136%
Half-life(h)	2.193±0.076	2.114±0.076	1.04	94.8.113%
Elim. rate constant (h^{-1})	0.328±0.010	0.338±0.010	0.97	89.7-105%
$LNAUC_{0-t}$	6.141±0.021	6.121±0.021	1.00	96.8-107%
$LNAUC_{0-inf}$	6.171±0.019	6.149±0.019	1.00	97.3-107%
LNC_{max}	4.654±0.018	4.611±0.018	1.01	99.9-109%

Table 5

Test/Reference Ratio for Pharmacokinetic Parameters in Individual Subjects

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1			
2	2			
3	2			
4	2			
5	1			
6	2			
7	1			
8	2			
9	1			
10	1			
11	2			
12	1			
13	1	(b)4 - Confidential Business		
14	1			
15	2			
16	1			
17	2			
18	2			
19	2			
20	1			
21	1			
22	1			
23	2			
24	2			
25	1			
26	2			
Mean		1.01	1.00	1.02
Range		(0.71-1.45)	(0.72-1.43)	(0.83-1.32)

- The elimination rate constant and thus AUC_{0-inf} could not be calculated for this subject

Table 6

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1	0.98	0.98
2	0.97	0.98
3	0.98	0.96
4	0.98	0.97
5	0.98	0.98
6	0.96	0.96
7	0.97	0.98
8	0.96	0.97
9	0.96	0.95
10	0.92	0.93
11	0.98	0.96
12	0.96	0.98
13	0.95	0.98
14	0.97	0.97
15	0.97	0.97
16	0.96	0.98
17	0.99	0.97
18	0.98	0.98
19	0.97	0.98
20	0.97	0.97
21	0.97	0.97
22	0.95	-
23	0.95	0.97
24	0.97	0.95
25	0.92	0.90
26	0.96	0.99

- The elimination rate constant and thus AUC_{0-inf} could not be calculated for this subject

Table 7

Quantitative Composition of Methylprednisolone Tablets USP

Ingredient	Amount/Tablet (mg)
Methylprednisolone, USP	4.04*
Microcrystalline Cellulose, NF	(b)4 - Confidential Business
Lactose Monohydrate, NF	
Pregelatinized Starch, NF	
(b)4 -	
Magnesium Stearate, NF	
Total	100.00

* contains 1% overage

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Methylprednisolone Tablets
Dose Strength: 4 mg
ANDA No.: 40-194
Firm: Invamed Inc.
Submission Date: June 18, 1996
File Name: 40194SD.696

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT (b)4 (Q) in 30 minutes USP method
Reference Drug: Medrol Tablets (Upjohn)
Assay Methodology (b)4 -

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # D951204 Strength(mg) 4			Reference Product Lot # 244MJ Strength(mg) 4		
	Mean %	Range	%CV	Mean %	Range	%CV
10	86.2	(b)4 - Confidential Business	2.3	93.7	(b)4 - Confidentia Business	12.5
20	92.0		1.1	102.6		3.5
30	92.9		1.1	102.7		1.8
40	93.3		1.1	102.7		1.9

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

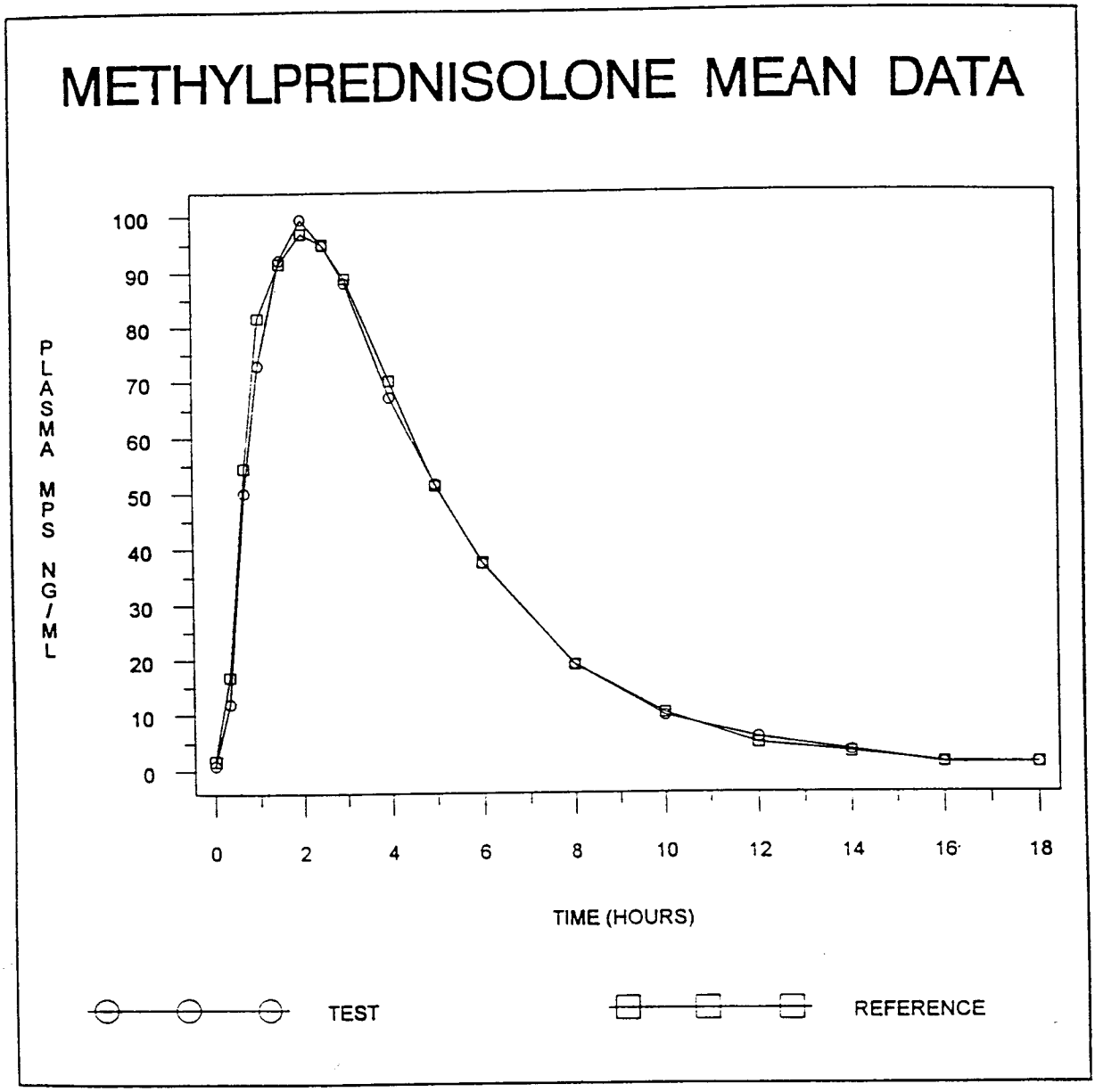


Figure 1

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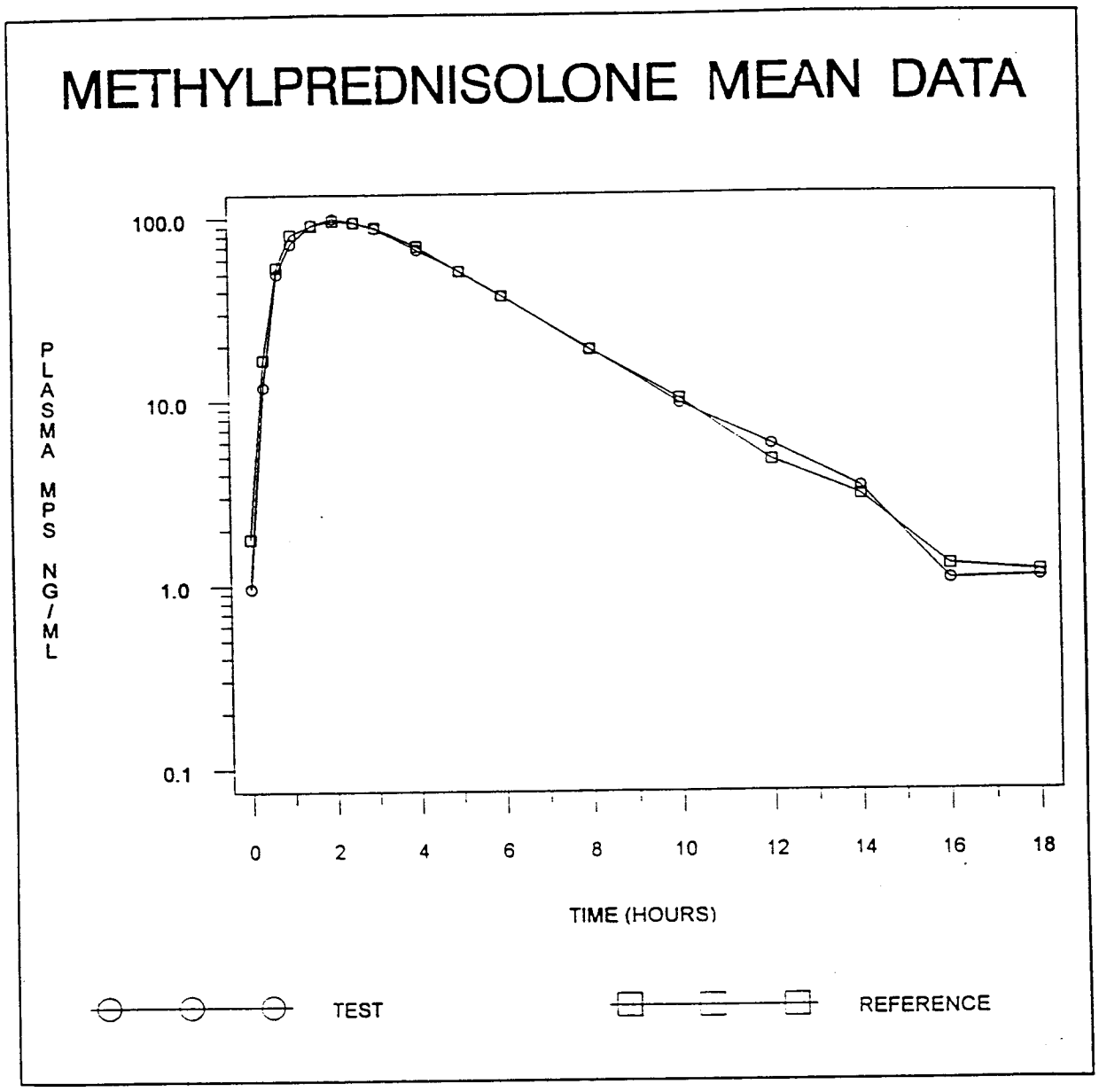

figure 2

000128

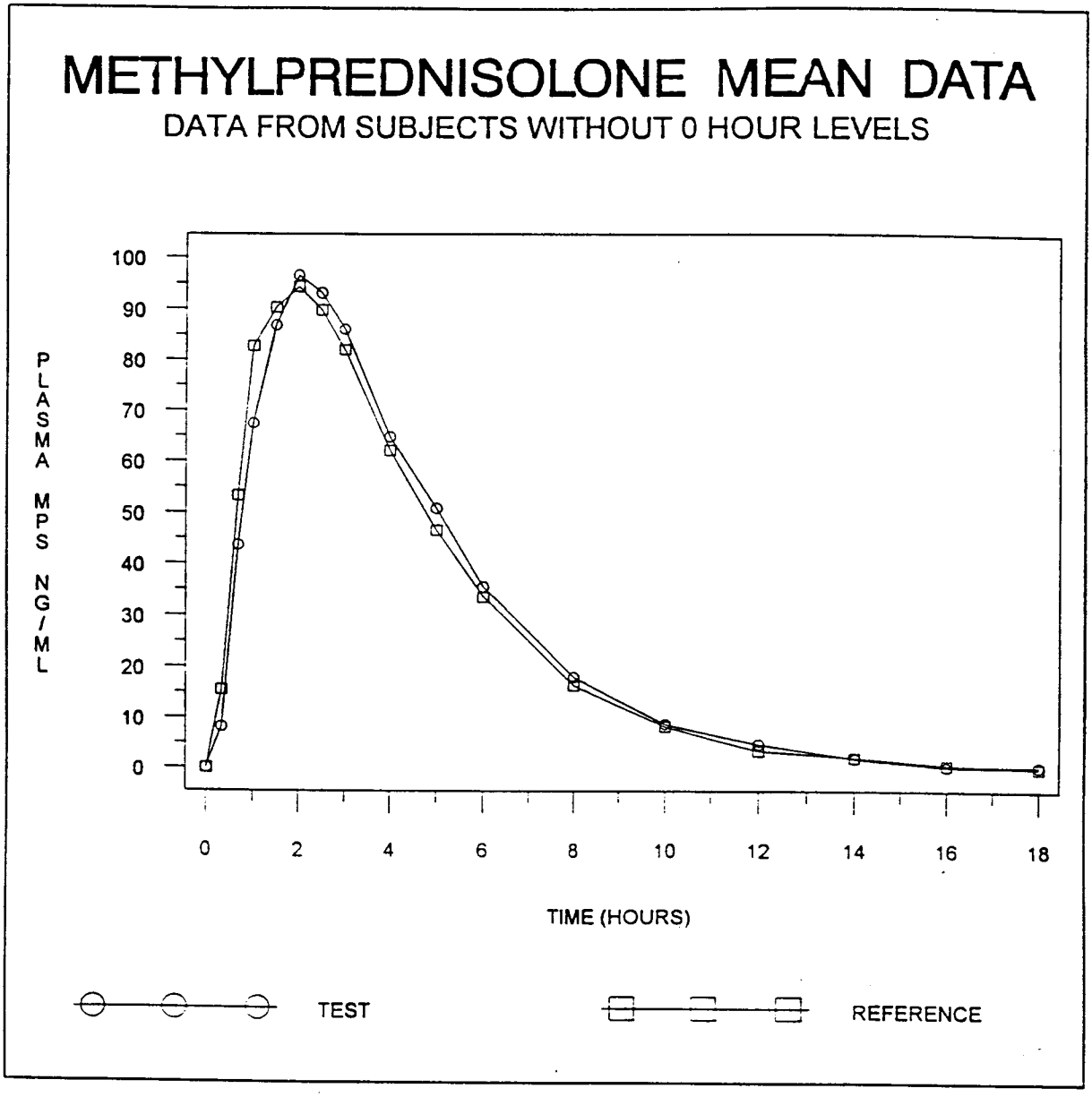

figure 3

000129

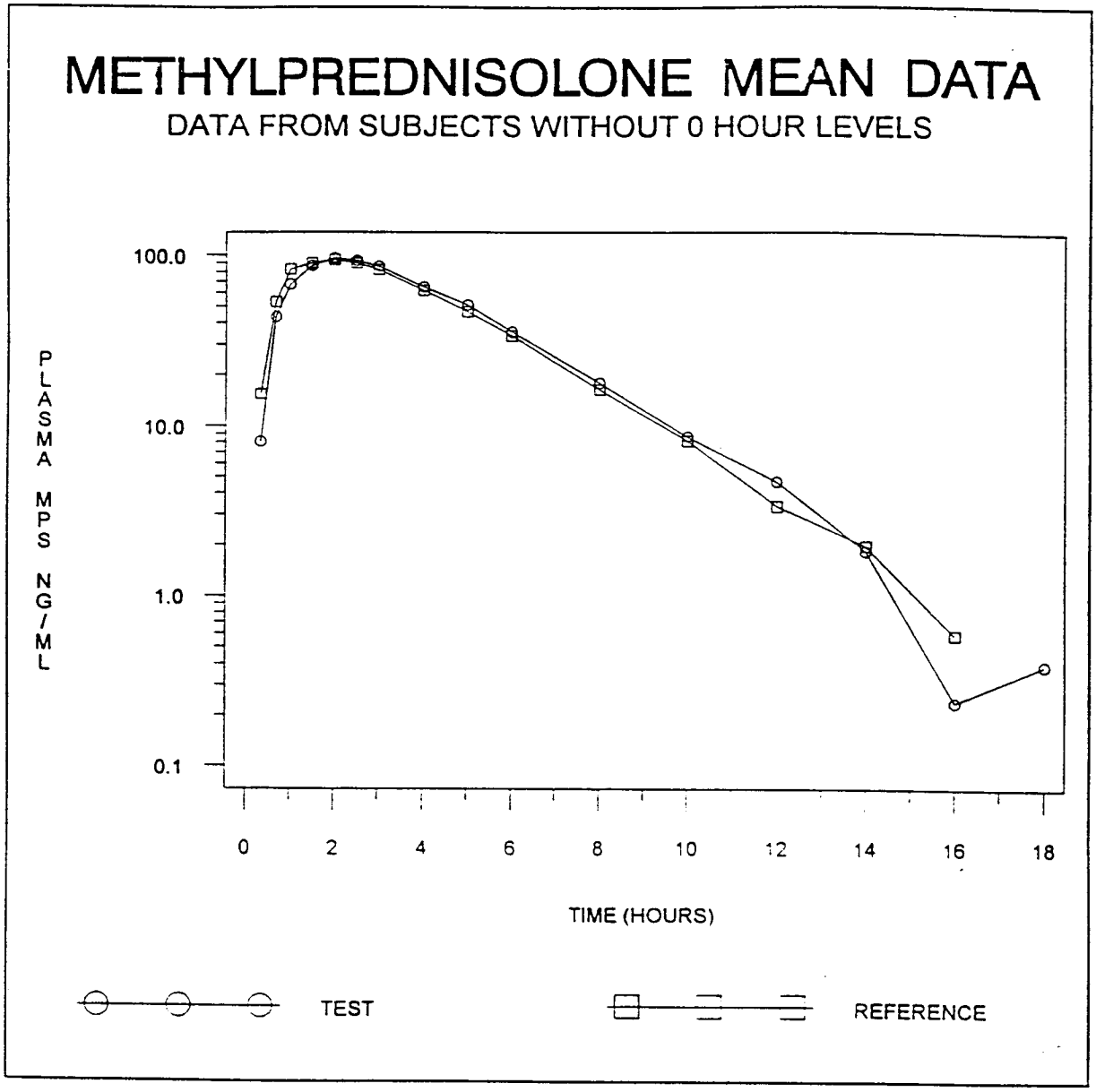

Figure 1

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