CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-612

***Name*:** Methylprednisolone Sodium Succinate for Injection USP, 1 gram (base)/vial

***Sponsor*:** American Pharmaceutical Partners, Inc.

***Approval Date*:** August 12, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

APPROVAL LETTER

ANDA 40-612

AUG 12 2004

American Pharmaceutical Partners, Inc.
Attention: Kathleen Dungan
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 16, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Methylprednisolone Sodium Succinate for Injection USP, 1 gram (base)/vial.

Reference is also made to your amendments dated August 2, and August 5, 2004.

We note that Center Director has determined that your ANDA is for a medically necessary drug product for which a market shortage currently exists. As a result, your ANDA has been granted expedited review status.

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 Methylprednisolone Sodium Succinate for Injection USP, 1 gram (base)/vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Solu-Medrol® for Injection, 1 gram (base)/vial, of Pharmacia and Upjohn Co.).

Under Section 506A of the Act, 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 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 8/12/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-612
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/S.Patankar 8/12/04
HFD-645/S.Liu S.H. Liu 8/12/04
HFD-617/W.Pamphile 8/12/04
HFD-613/P.Birch
HFD-613/J.Grace 8/12/04

Robert Lee Lent
8/12/2004

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APPROVAL

PS 8/12/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

LABELING

AMERICAN PHARMACEUTICAL PARTNERS, INC.

451013/Issued: July 2004

METHYLPREDNISOLONE SODIUM SUCCINATE

FOR INJECTION, USP

For Intravenous or Intramuscular Administration

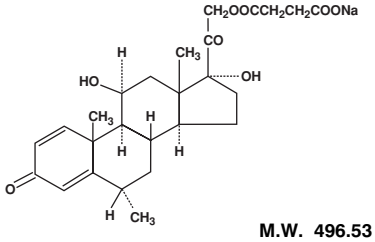
Rx only

DESCRIPTION:

Methylprednisolone Sodium Succinate for Injection, USP sterile powder contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is pregna-1,4-diene-3,20-dione, 21-(3-carboxy-1-oxopropoxy)-11, 17-dihydroxy-6-methyl-monosodium salt, (6α, 11β).

The structural formula is:



M.W. 496.53

Methylprednisolone sodium succinate is so extremely soluble in water that it may be administered in a small volume of diluent and is especially well suited for intravenous use in situations in which high blood levels of methylprednisolone are required rapidly.

Methylprednisolone Sodium Succinate for Injection, USP is available in a 1 gram vial for intravenous or intramuscular administration.

1 g (Multiple Dose Vial) Each 16 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 1 g methylprednisolone; also, 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8 and the tonicity for the 1 g per 16 mL solution is 0.40 osmolar. (Isotonic saline = 0.28 osmolar).

IMPORTANT - Use only Bacteriostatic Water For Injection with Benzyl Alcohol when reconstituting Methylprednisolone Sodium Succinate for Injection, USP.

Use within 48 hours after mixing.

CLINICAL PHARMACOLOGY:
Methylprednisolone is a potent anti-inflammatory steroid with greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of methylprednisolone and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

INDICATIONS AND USAGE:
When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, Methylprednisolone Sodium Succinate for Injection, USP is indicated for intravenous or intramuscular use in the following conditions:

1. Endocrine Disorders
- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)
- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)
- Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
- 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:
- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Epicondylitis
- Acute nonspecific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Acute and subacute bursitis

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
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrheic dermatitis
- Severe psoriasis
- Mycosis fungoides

5. Allergic States
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Serum sickness
- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Urticarial transfusion reactions
- Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

6. Ophthalmic Diseases
Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- Herpes zoster ophthalmicus
- Iritis, iridocyclitis
- Chorioretinitis
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Sympathetic ophthalmia
- Anterior segment inflammation
- Allergic conjunctivitis
- Allergic corneal marginal ulcers
- Keratitis

7. Gastrointestinal Diseases
To tide the patient over a critical period of the disease in:
- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

8. Respiratory Diseases

Symptomatic sarcoidosis
Berylliosis
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate anti-tuberculous chemotherapy
Loeffler's syndrome not manageable by other means
Aspiration pneumonitis

9. Hematologic Disorders

Acquired (autoimmune) hemolytic anemia
Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)
Secondary thrombocytopenia in adults
Erythroblastopenia (RBC anemia)
Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults
Acute leukemia of childhood

11. 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

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 neurologic or myocardial involvement

CONTRAINDICATIONS:

The use of Methylprednisolone Sodium Succinate for Injection, USP is contraindicated in premature infants because the 1 g multiple dose vial when reconstituted will contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Methylprednisolone Sodium Succinate for Injection, USP is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS:

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

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

A study has failed to establish the efficacy of methylprednisolone in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with methylprednisolone may increase the risk of mortality in certain patients (i.e., patients with elevated serum creatinine levels or patients who develop secondary infections after methylprednisolone).

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.

Average and large doses of cortisone or hydrocortisone 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 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 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.

Because rare instances of anaphylactic (e.g., bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate

precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of methylprednisolone (greater than 0.5 gram administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

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 child-bearing 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.

PRECAUTIONS:

General Precautions

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.

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.

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.

Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

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
Severe arthralgia
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones
Osteoporosis

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatologic

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

Neurological

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

Endocrine

Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Menstrual irregularities
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

Metabolic

Negative nitrogen balance due to protein catabolism

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Hyperpigmentation or hypopigmentation
Subcutaneous and cutaneous atrophy
Sterile abscess
Anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm
Urticaria
Nausea and vomiting
Cardiac arrhythmias; hypotension or hypertension

DOSAGE AND ADMINISTRATION:

When high dose therapy is desired, the recommended dose of Methylprednisolone Sodium Succinate for Injection, USP is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4 to 6 hours for 48 hours.

In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours.

Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

In other indications initial dosage will vary from 10 to 40 mg of methylprednisolone depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy.

Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

Methylprednisolone Sodium Succinate for Injection, USP may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, reconstitute the 1 g/vial product with 16 mL of Bacteriostatic Water for Injection with Benzyl Alcohol. The desired dose may be administered intravenously over a period of several minutes.

To prepare solutions for intravenous infusion, first prepare the solution for injection as directed. This solution may then be added to indicated amounts of 5% dextrose in water, isotonic saline solution or 5% dextrose in isotonic saline solution.

Multiple Sclerosis

In 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).

STORAGE CONDITIONS:

Protect from light.

Store unreconstituted product at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Store solution at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Use solution within 48 hours after mixing.

HOW SUPPLIED:

Product No.	NDC No.	
276530	63323-265-30	Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial (16 mL when mixed), multiple dose vial, packaged individually.

Vial stoppers do not contain natural rubber latex.

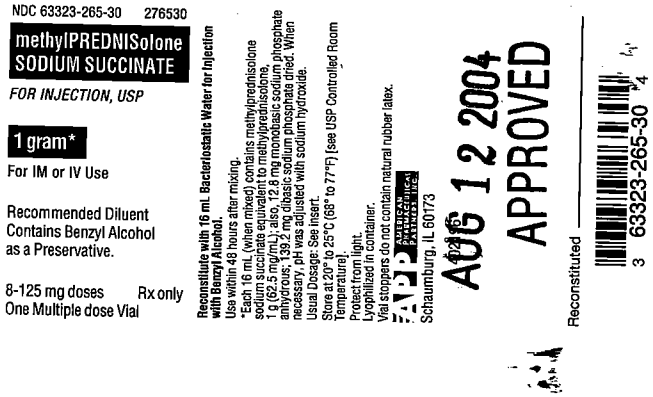
AMERICAN PHARMACEUTICAL PARTNERS, INC.
Schaumburg, IL 60173
451013
Issued: July 2004

40-612

Methylprednisolone Sodium Succinate for Injection, USP (MDV)

Labeling Amendment per 07/26/04 Deficiency Letter

Vial Label



40-612

Spec. No.: **7C**

methylPREDNISolone SODIUM SUCCINATE
FOR INJECTION, USP
1 gram*

APPROVED
AUG 12 2004

Reconstitute with 16 mL Bacteriostatic Water for Injection with Benzyl Alcohol.

*Each 16 mL (when mixed) contains methylprednisolone sodium succinate equivalent to methylprednisolone, 1 g (62.5 mg/mL); also, 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried. When necessary, pH was adjusted with sodium hydroxide.
Lyophilized in container.

Usual Dosage: See insert.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Schaumburg, IL 60173

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Use within 48 hours after mixing.

Protect from light.

Vial stoppers do not contain natural rubber latex.

AMERICAN PHARMACEUTICAL PARTNERS, INC.

NDC 63323-265-30 276530

methylPREDNISolone SODIUM SUCCINATE

FOR INJECTION, USP

1 gram*

For IM or IV Use

Recommended Diluent Contains Benzyl Alcohol as a Preservative.

8-125 mg doses
One Multiple dose Vial

Rx only

AMERICAN PHARMACEUTICAL PARTNERS, INC.

N 63323-265-30 4

62838

BLACK 323C

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	40-612
Date of Submission:	June 16, 2004
Applicant's Name:	American Pharmaceutical Partners, Inc.
Established Name:	Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial

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Labeling Deficiencies:

1. CONTAINER (1 g/vial [16 mL when mixed])
   a. Add "Recommended Diluent Contains Benzyl Alcohol as a Preservative" to the principal display panel to be consistent with the RLD.
   b. Revise "16 mL Multiple Dose vial" to read:

      "8-125 mg doses
      One Multiple dose Vial"

2. CARTON (1 vial)
   a. Refer to CONTAINER comments 1.a. and 1.b.
   b. Back Panel: "...16 mL Bacteriostatic Water..." [correct spelling of "Bacteriostatic"]
   c. Side Panel: "Use within 48 hours after mixing"

3. PROFESSIONAL INSERT
   a. DESCRIPTION
      i. Fourth paragraph: "...1 gram vial for..."
      ii. Sixth paragraph: "...the tonicity for the 1 g per 16 mL solution is 0.40 osmolar...."
   b. HOW SUPPLIED: "...1 g/vial (16 mL when mixed), multiple dose vial..."

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

http://www.fda.gov/cder/guidance/5004fnl.htm.

Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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.

John J Grunford

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? There is a warning in the D&A section	x		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study			

acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST:
There is a claim on the container/tray label that "Vial stoppers do not contain natural latex rubber". Is this an accurate statement?

FOR THE RECORD:

GRANTED EXPEDITED REVIEW

1. MODEL LABELING -
   The RLD is Solu-Medrol® (by Pharmacia and Upjohn; NDA 11-856. There are several SLR supplements [redacted] The most recently approved insert labeling is NDA 11-856/S-077 approved September 4, 1991. I used the insert labeling approved on September 4, 1991 for the model labeling except for the additional information in the WARNINGS and PRECAUTIONS sections that was approved for another generic application, ANDA 85-855/S-030, on March 25, 1994 (based on the December 23, 1993 coverletter for this supplement [Vol. A5.1], the changes were requested by the Agency)
   - From regulatory checklist: "RLD provided Benzyl Alcohol in a separate co-vial. Refer to ANDA # 40-583; firm does not have to provide Benzyl Alcohol. Labeling gives instructions to reconstitute with Bacterostatic Water/Benzyl Alcohol."
   - USP: Packaging and storage-Preserve in Containers for Sterile Solids as described under Injections
   - Related ANDA 40-583: 40 mg/vial and 125 mg/vial

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 11-856

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	PI [vol. A1.1, pg. 12]	None

Exclusivity Data For NDA 11-856

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

3. MANUFACTURING FACILITY (Vol. A1.1, pg. 192)
   American Pharmaceutical Partners, Inc.
   2020 Ruby Street
   Melrose Park, IL 60160

4. STORAGE CONDITIONS:
   RLD – Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Protect from light.
   ANDA – Same as RLD

5. DISPENSING RECOMMENDATIONS:
   RLD -None
   ANDA – None

6. COMPOSITION:

Ingredient	1 g/vial
Methylprednisolone [redacted]	[redacted] equivalent to 1 g methylprednisolone)
Monobasic Sodium	12.8 mg
Dibasic Sodium Phosphate	139.2 mg
Sodium Hydroxide	q.s. [redacted] if necessary, to adjust pH

[Vol. A1.1, pg. 75]

7. PRODUCT LINE:
   RLD- 1 g vial
   1 g vial with diluent
   1 g vial with diluent and IV Administration set
   1 g Act-o-vial system (single -dose vial)
   RLD also marketed in other strengths

   ANDA- 1 g/vial (16 mL when mixed), multiple dose vial, packaged individually [does not provide diluent]
   The following are subject of related ANDA 40-583:
   - 40 mg/vial (1 mL constituted solution), single dose vial, in packages of 25
   - 125 mg/vial (2 mL constituted solution), single dose vial, in packages of 25

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.3, pg. 667)
   Vial: 30 mL type 1 glass vial (product not light sensitive-see Note to the chemist for related ANDA 40-583)
   USP – Packaging and storage— Preserve in Containers for Sterile Solids as described under *Injections* <1>

9. PRODUCT DESCRIPTION:
   Finished Product COA-White or nearly white powder in a 30-mL flint vial [Vol A1.3, pg. 729]

10. BIOEQUIVALENCE and MICROBIOLOGY: Under review

Date of Review: July 22, 2004 Date of Submission: June 16, 2004

Primary Reviewer: Ruby Wu RWu Date: 7/22/04

Team Leader: John Grace John Grace Date: 7/23/04

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cc: ANDA: 40-612
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	40-612
Date of Submission:	August 5, 2004
Applicant's Name:	American Pharmaceutical Partners, Inc.
Established Name:	Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial

---

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

1. CONTAINER (1 g/vial [16 mL when mixed])

   Satisfactory in FPL as of August 5, 2004 paper submission. (Vol. 2.1)

2. CARTON (1 vial)

   Satisfactory in FPL as of August 5, 2004 paper submission. (Vol. 2.1)

3. PROFESSIONAL INSERT

   Satisfactory in FPL as of August 5, 2004 paper and electronic submissions. (Vol. 2.1 and \\Cdsesubogd1\n40612\N_000\2004-08-05\451013 FPL.pdf)

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Solu-Medrol®
RLD NDA Number: NDA 11-856
RLD NDA Drug Name: Methylprednisolone Sodium Succinate for Injection
RLD NDA Firm: Pharmacia and Upjohn
Date of Approval of NDA Insert and supplement: NDA 11-856/S-077 approved September 4, 1991
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with RLD labels in drug folder.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? There is a warning in the D&A section	x		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST:

There is a claim on the container/tray label that "Vial stoppers do not contain natural latex rubber". Is this an accurate statement?

FOR THE RECORD:

GRANTED EXPEDITED REVIEW

1. MODEL LABELING -
   The RLD is Solu-Medrol® (by Pharmacia and Upjohn; NDA 11-856. There are several SLR supplements [redacted]. The most recently approved insert labeling is NDA 11-856/S-077 approved September 4, 1991. I used the insert labeling approved on September 4, 1991 for the model labeling except for the additional information in the WARNINGS and PRECAUTIONS sections that was approved for another generic application, ANDA 85-855/S-030, on March 25, 1994 (based on the December 23, 1993 coverletter for this supplement [Vol. A5.1], the changes were requested by the Agency)
   - From regulatory checklist: "RLD provided Benzyl Alcohol in a separate co-vial. Refer to ANDA # 40-583; firm does not have to provide Benzyl Alcohol. Labeling gives instructions to reconstitute with Bacterostatic Water/Benzyl Alcohol."
   - USP: Packaging and storage-Preserve in Containers for Sterile Solids as described under Injections
   - Related ANDA 40-583: 40 mg/vial and 125 mg/vial

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 11-856

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	PI [vol. A1.1, pg. 12]	None

Exclusivity Data For NDA 11-856

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired exclusivities	N/A	None

3. MANUFACTURING FACILITY (Vol. A1.1, pg. 192)
   American Pharmaceutical Partners, Inc.
   2020 Ruby Street
   Melrose Park, IL 60160

4. STORAGE CONDITIONS:
   RLD – Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Protect from light.
   ANDA – Same as RLD

5. DISPENSING RECOMMENDATIONS:
   RLD -None
   ANDA – None

6. COMPOSITION:

Ingredient	1 g/vial
Methylprednisolone [redacted]	[redacted] (equivalent to 1 g methylprednisolone)
Monobasic Sodium	12.8 mg
Dibasic Sodium Phosphate	139.2 mg
Sodium Hydroxide	q.s. [redacted] if necessary, to adjust pH

[Vol. A1.1, pg. 75]

7. PRODUCT LINE:
   RLD- 1 g vial
   1 g vial with diluent
   1 g vial with diluent and IV Administration set
   1 g Act-o-vial system (single -dose vial)
   RLD also marketed in other strengths

   ANDA- 1 g/vial (16 mL when mixed), multiple dose vial, packaged individually [does not provide diluent]
   The following are subject of related ANDA 40-583:
   - 40 mg/vial (1 mL constituted solution), single dose vial, in packages of 25
   - 125 mg/vial (2 mL constituted solution), single dose vial, in packages of 25

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.3, pg. 667)
   Vial: 30 mL type 1 glass vial (product not light sensitive-see Note to the chemist for related ANDA 40-583)
   USP – Packaging and storage— Preserve in Containers for Sterile Solids as described under *Injections* <1>

9. PRODUCT DESCRIPTION:
   Finished Product COA-White or nearly white powder in a 30-mL flint vial [Vol A1.3, pg. 729]

10. BIOEQUIVALENCE and MICROBIOLOGY: Under review

Date of Review: July 22, 2004 Date of Submission: August 5, 2004

Primary Reviewer: Postelle Birch for Ruby Wu Date: 8/12/2004

Team Leader: John Grace Date: 8/12/04

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cc: ANDA: 40-612
DUP/DIVISION FILE
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

CHEMISTRY REVIEW

ANDA 40-612

Methylprednisolone Sodium Succinate For Injection USP, 1-g Multiple Dose Vial

American Pharmaceutical Partners, Inc.

Suhas Patankar, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-612

2. REVIEW #: 1

3. REVIEW DATE: July 21, 2004

4. REVIEWER: Suhas Patankar, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Firm	**Document Date**
Original ANDA Submission	June 16, 2004
Agency	**Document Date**
Agency Acknowledgement Letter (Acceptable for filing: June 17, 2004)	June 28, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	American Pharmaceutical Partners, Inc.
Address:	2045 North Cornell Avenue Melrose Park, IL 60160
Representative:	Kathleen Dungan
Telephone/Fax:	708-486-2024 / 708-343-4269

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Methylprednisolone Sodium Succinate for Injection

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for American Pharmaceutical Partners (APP), Inc.'s proposed ANDA for Methylprednisolone Sodium Succinate for Injection, 1-g multiple dose vial is the approved, referenced listed drug, Solu-Medrol® Sterile Powder of NDA # 11856 006 (Approved Prior to January 1, 1982), held by Pfizer (previously Pharmacia & Upjohn).

b. In accordance with Food Drug and Cosmetic Act as amended in September 24, 1984 patent and exclusivity data published in the "Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Version, obtained from the FDA website, APP, Inc. states there is no patent or exclusivity.

c. The applicant provided paragraph I certification.

10. PHARMACOL. CATEGORY:

Methylprednisolne is a glucocorticoid used as an anti-inflammatory agent.

11. DOSAGE FORM: Sterile Powder

12. STRENGTH/POTENCY: 1-g / Vial

13. ROUTE OF ADMINISTRATION: IM; IV Injection

14. Rx/OTC DISPENSED: _X__Rx __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

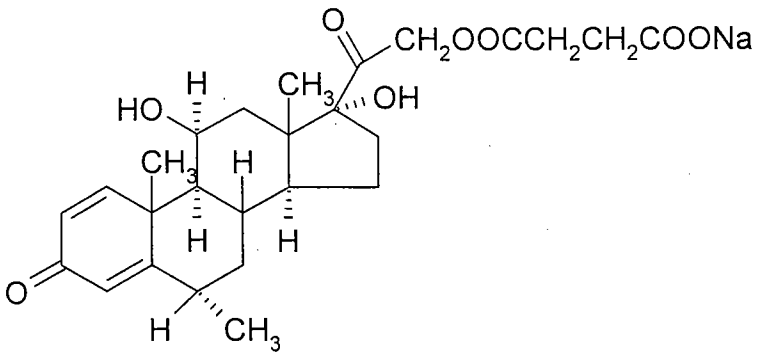
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Methylprednisolone Sodium Succinate

Chemical Formula:	$C_{26}H_{33}NaO_8$
CAS Number:	2375-03-3
Molecular Weight:	496.63
Chemical Name:	Pregna-1,4-diene-3,20-dione, 21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl - monosodium salt, (6α,11β).



Note :

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	7/14/04	Reviewed by S. Patankar
	III			4			
	III			4			
	III			4			
	V			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

The firm states that DMF letters are not required for the packaging seals as per OGD recommendation for ANDA submission for parenterals.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	85-852	Approved on 1/1/82 (Methylprednisolone Sodium Succinate for Injection by Hospira)
ANDA	89-174	Approved on 8/18/87 (Methylprednisolone Sodium Succinate for Injection by Hospira)
ANDA	40-583	Pending approval 9Methylprednisolone Sodium Succinate for Injection by APP

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	8/9/04	N. Nath
EES	Acceptable	8/3/04	S. Adams
Methods Validation	Not needed based on the current OGD guidelines on method validation		
Labeling	Acceptable	8/12/04	R. Wu
Bioequivalence	Acceptable	8/4/04	E. Stier
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below:

Review of Original ANDA's for Methylprednisolone Sodium Succinate for Injection, has been approved for expedited review as these products are recommended and determined to be medically necessary by the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products for treatment of severe allergic reactions, adrenocortical insufficiency and autoimmune diseases. At present no generic firms are manufacturing the drug product and the innovator Pfizer is unable to meet market demand.

The Chemistry Review for ANDA 40-612

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Methylprednisolone Sodium Succinate is a synthetic analog of naturally occurring glucocorticoids hydrocortisone and cortisone. It is a white or nearly white odorless hygroscopic amorphous solid. It is freely soluble in water and alcohol but is insoluble in chloroform and very slightly soluble in acetone. The compound is dextrorotatory and melts at over 300 °C.

Note : [redacted]

Drug Product:

Methylprednisolone Sodium Succinate for Injection is a sterile powder, when reconstituted with bacteriostatic water for injection with Benzyl Chloride it can be administered by intravenous or intramuscular injection or intravenous infusion. These synthetic analogs of glucocorticoids have potent anti-inflammatory effects in disorders of many organ systems. This analog exhibits greater anti-inflammatory potency than prednisolone and has less tendency to induce sodium and water retention.

The applicant has [redacted] Methylprednisolone Sodium Succinate for Injection is available for IV and IM use. The lyophilized solid is provided in a 16 mL

flint glass vials with a gray lyophilization stopper and aluminum crimp cap with a light blue bonnet. The 1 g multiple dose vial is reconstituted to 16 mL at the time of administration. The applicant does not provide the diluent like the RLD.

For the 1 g multiple dose vial each 16 mL (62.5 mg/mL) when mixed as directed contains Methylprednisolone Sodium Succinate equivalent to 1 g methylprednisolone; 12.8 mg of monobasic sodium phosphate anhydrous, 139.2 mg of dibasic sodium phosphate dried, and benzyl alcohol.

In addition, the firm states the pH of the solution is adjusted with NaOH between 7 and 8 and the tonicity is 0.4 osmolar.

The high dose of Methylprednisolone Sodium Succinate, USP for injection is 30 mg/Kg. if desired this can be repeated every 4 to 6 hours. Therefore the maximum daily dose (MDD) is above 2 g.

B. Description of How the Drug Product is Intended to be Used

IM and IV Injection

C. Basis for Approvability or Not-Approval Recommendation

Approvable.

CMC Acceptable
Bio - Acceptable
EER – Acceptable
Microbiology – Acceptable

III. Administrative

A. Reviewer's Signature

8/12/04

B. Endorsement Block

S. Patankar, Ph.D./ 8/12/04
S. Liu, Ph.D./ S.H. Liu 8/12/04
W. Pamphile, Pharm.D./ 8/12/04 for

C. CC Block

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

30. MICROBIOLOGY

Acceptable on 8/9/04 by N. Nath.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

As per current OGD guidelines no methods validation is needed.

32. LABELING

NOTE for Labeling Reviewer: The RLD provides the diluents for the 1 g multiple dose vials. The ANDA holder states that it does not include the diluent. Labeling reviewer has been contacted.

Response : Labeling reviewer stated this was acceptable.

Acceptable on 8/12/04 by R. Wu.

33. ESTABLISHMENT INSPECTION

Acceptable on 8/3/04 by S. Adams.

34. BIOEQUIVALENCE

Acceptable on 8/4/04 by E. Stier.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

APP requests a categorical exclusion from requirement as per 21 CFR § 25.31(a) (p. 01119). The applicant has submitted certification of compliance with federal/state/local law.

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 / S. Patankar, Ph.D. / 8/2/04

HFD-620 / S. Liu, Ph.D. / S.H. Liu 8/12/04

HFD-617 / W. Pamphile, PharmD. / 8/12/04 for

F/T by

V:\FIRMSAM\APP\LTRS&REV\40612.CR01.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-612
Drug Product Name	Methylprednisolone Sodium Succinate for Injection , USP
Strength	1 g vial
Applicant Name	American Pharmaceuticals Partners, Inc.
Address	2045 North Corneil Avenue Melrose Park, IL 60160
Submission Date(s)	June 16, 2004
Amendment Date(s)	NA
Reviewer	Ethan M. Stier
First Generic	No
File Location	V:\firmsam\app\ltrs&rev\40612W0604.doc

I. Executive Summary

This application consisted of a request for waiver of *in* vivo bioequivalence study requirements for the test product, Methylprednisolone Sodium Succinate for Injection, USP, 1 gram vial. The reference listed drug is Solu-Medrol® 1 gram, manufactured by Pfizer (NDA 11-856). Based on the information submitted, the test product is acceptable under 21 CFR §320.24 (b)(6) of the Bioavailability/Bioequivalence Regulations.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Methylprednisolone Sodium Succinate For Injection, USP, 1 g vial
Reference Product	Solu-Medrol® 1 g vial
RLD Manufacturer	Pfizer
NDA No.	11-856
RLD Approval Date	The original NDA for methylprednisolone sodium succinate was filed on 02/13/59 and approved on 11/20/64. The entry in COMIS which matches the drug product referenced in this application lists a received date of 08/28/85, there is no further information listed.
Indication	Used primarily as an anti-inflammatory and immunosuppressive agent. When oral therapy is not feasible, Solu-Medrol Sterile powder is indicated for intravenous or intramuscular treatment of endocrine disorders, rheumatic disorders, collagen disease, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states and acute exacerbations of multiple sclerosis.

B. PK/PD Information

Bioavailability N/A

Food Effect N/A

Tmax 1 – 2 hours

Metabolism Liver (inactive metabolites)

Excretion Renal

Half-life 18 – 36 hours (biological half-life)

Relevant OGD or DBE History DBE has previously approved an ANDA (40-583) for methylprednisolone sodium succinate for injection

[redacted]

Refer to **V:\firmsam\APP\ltrs&rev\40583W0204.doc** list of previously reviewed ANDA's.

Methylprednisolone Sodium Succinate is a DESI drug.

Agency Guidance None

Drug Specific Issues (if any) None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	NA
Single-dose fed	No	NA
In vitro dissolution	No	NA
Waiver requests	Yes	1
Amendments	No	NA

D. Pre-Study Bioanalytical Method Validation

N/A

E. In Vivo Studies

N/A

F. Formulation

Location in appendix	Section I.A, Page 6
Inactive ingredients within IIG Limits (yes or no)	Yes
If yes, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

G. Waiver Request(s)

Strengths for which waivers requested	1 gm
Regulations cited	21 CFR §320.24 (b)(6) and 21 CFR §314.94(a)(9)(iii)
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	N/A
Waiver granted (yes or no)	Yes

H. Comments

1. The test product, Methylprednisolone Sodium Succinate for Injection, USP, 1 gram, is a sterile powder intended solely for administration by injection upon reconstitution and contains qualitatively the same active ingredient as the reference product. However, the buffer ingredients for the test product are qualitatively different from those contained in the RLD; a qualitative change in buffering agent is acceptable under 21 CFR §314.94(a)(9)(iii).

2. The Division of Chemistry has found the ——— active and inactive ingredients in the test product to be acceptable (See V:\FIRMSAM\APP\LTRS&REV\40612.CR01.DOC).

3. The test product is acceptable under 21 CFR 320.24(b)(6).

I. Recommendations

The information submitted by American Pharmaceutical Partners on Methylprednisolone Sodium Succinate For Injection, USP, 1 g/vial falls under 21 CFR 320.24(b)(6) of the Bioavailability/Bioequivalence regulations. From the bioequivalence point of view, the Division of Bioequivalence deems the test product (Sodium Succinate For Injection, USP, 1 g/vial) to be bioequivalent to Solu-Medrol® Injection, 1 g/vial, manufactured by Pfizer.

Ethan M. Stier, Ph.D.
Review Branch II
Division of Bioequivalence

Ethan M Stier 8/3/04

RD INITIALED GJP Singh, Ph.D.
FT INITIALED GJP Singh, Ph.D. Date 8-3-04

cc: ANDA# 40-612 (original, duplicate), Stier, HFD-650, Singh, HFD-658, Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-612 APPLICANT: APP

DRUG PRODUCT: Methylprednisolone Sodium Succinate For Injection, USP 1 gram

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

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit

for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #40-612
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: E. Stier

V:\FIRMSAM\APP\LTRS&REV\40612W0604.DOC
Printed in final on 08/03/04

Endorsments: (Final with Dates)
HFD-658/ E. Stier 8/03/04
HFD-658/ GJP. Singh 8-3-04
HFD-650/ D. Conner 8/4/04
HFD-617/ B. Fritsch

Bioequivalence - Acceptable

Submission Dates: 06/04

1) Waiver (WAI)

Strength: 1 gram
Outcome: **AC**

Outcome Decisions: AC- Acceptable
Winbio comments: Waiver is granted

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-612 SPONSOR : APP

DRUG AND DOSAGE FORM : METHYLPREDNISOLONE SODIUM SUCCINATE for INJECTION

STRENGTH(S) : 1 GRAM

TYPES OF STUDIES : NA

CLINICAL STUDY SITE(S) : NA

ANALYTICAL SITE(S) : NA

STUDY SUMMARY : NA

DISSOLUTION : NA

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic ___	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause ____		
Other ____		

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____ No_____ N/A
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)
DBE Dissolution Method and Spec acknowledged by firm: Yes _____

PROJECT MANAGER: _____ DATE:_____

PRIMARY REVIEWER : Ethan M. Stier, Ph.D. BRANCH: II

INITIAL : Ethan M Stier DATE : 8/3/04

TEAM LEADER : GJP Singh, Ph.D. BRANCH: II

INITIAL GJP Singh DATE : 8.3.04

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : Barbara M Davit DATE : 8/4/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-620

26 July 2004

ANDA: 40-612

Drug Product Name
Proprietary: N/A
Non-proprietary: Methylprednisolone Sodium Succinate for injection, USP
Drug Product Classification: None.

Review Number: #1

Subject of this Review
Submission Date: June 16, 2004
Receipt Date: June 17, 2004
August 2, 2004 (Response to telecon July 26, 2004)
Consult Date: N/A
Date Assigned for Review: July 21, 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: American Pharmaceutical Partners, Inc.
Address: 2045 N. Cornell Ave., Melrose Park, IL 60160
Representative: Kathleen Dungan, Senior Regulatory Scientist
Telephone: 708-486-2024

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:**
American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 1g in 30-mL multi-dose glass vial as lyophilized powder; I/V.

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** Anti-inflammatory steroid.

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The subject ANDA is similar in its sterility assurance to ANDAs 76-235 (April 2002) and ANDA 76-573 (August 2003) by the subject reviewer; significant parts of the current review are taken from the previous reviews and modified and updated as appropriate.

The applicant's response to telecon of July 26, 2004, regarding preservative effectiveness, initiated by the subject reviewer, is contained in their response dated August 2, 2004; response has been incorporated in the review.

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment".

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

[ ]

B. Brief Description of Microbiology Deficiencies -
None

C. Assessment of Risk Due to Microbiology Deficiencies -
N/A.

III. Administrative

A. Reviewer's Signature Nrapendra Nath 8/9/2004

B. Endorsement Block
Microbiologist / Nrapendra Nath
Microbiology Team Leader/Neal J. Sweeney

C. CC Block
Neal J Sweeney 8-9-04
cc:
Original ANDA
HFD- 600/Division File
Field Copy

filename: V:\Microrev\ 40-612.doc

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information from

MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

ADMINISTRATIVE DOCUMENTS

ANDA 40-612

Date: August 25, 2003

From: Harvey Greenberg
Drug Shortage Coordinator
Division of Labeling and Program Support

To: Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Through: Gary Buehler
Director
Office of Generic Drugs

Subject: Request to Expedite the Review of Original Abbreviated New Drug Applications (ANDAs) for Methylprednisolone Sodium Succinate Injection Products

This memorandum is to request your concurrence to expedite the review of origin ANDAs for Methylprednisolone Sodium Succinate Injection (Solu-Medrol). These products are recommended and determined to be medically necessary by the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, HFD-550 for the treatment of severe allergic reactions, adrenocortical insufficiency and autoimmune diseases. At present no generic firms are manufacturing the drug product and the innovator Pfizer is unable to meet market demand. There has been an ongoing nation-wide shortage. In order to build adequate inventory it is necessary to grant expedited reviews for any original ANDA submitted for Methylprednisolone Sodium Succinate. OGD will proceed with the reviews and a facilitated approval process, if the application meets the necessary standards, in order to provide patients with a medically necessary approved drug product. Please note that we expect to receive several applications by the end of 2003.

✓ I concur _____ I do not concur

Janet Woodcock, M.D.

Record of Telephone Conversation:

Nrapendra Nath
Date: 7/26/2004 Time: 7/26/04

ANDA # 40-612

Drug: Methylprednisolone Sodium Succinate for Injection

Firm: American Pharmaceutical Partners

Contact Person: Kathleen Dungan, Sr. Regulatory Scientist
Telephone: 708-486-2024

Questions:
The drug product is provided as lyophilized powder in 30mL multi-dose vial; the drug product does not have bacteriostatic agent in its formulation; however, the package insert recommends that the WFI containing benzyl alcohol be used to reconstitute solution for injection. Please provide data showing preservative effectiveness of reconstituted solution at 48 hours or later.

Response:
She will get the data and send the response right away.

V:\Microrev\Telecons\40-612Tel Rec.doc

CC: ANDA 40-612
D:V - File

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-612 Applicant American Pharmaceutical Partnes, Inc.
Drug Methylprednisolone Sodium Succinate for Injection USP Strength(s) 1 g/vial

APPROVAL ■ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch
Date 11 Aug 2004 Initials MMS
Date 8/12/04 Initials for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 12-856
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter: PI Cert/No exclusivities ∴ Ready for Full Approval
Comments:

2. Project Manager, **Wanda Pamphile** Team 5
Review Support Branch
Date 8-10-04 Initials WP
Date 8-12-04 Initials WP

Original Rec'd date 6-16-04
Date Acceptable for Filing 6-17-04
Patent Certification (type) I
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 8-3-04
Date of Office Bio Review 8-4-04
Date of Labeling Approv. Sum 8-12-04
Date of Sterility Assur. App. 8-9-04
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☒ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐
OGD Regulatory Counsel, Post-MMA Language Included ☐
Comments:
N/A
Date
Initials

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:
Date 8/12/04 Initials PS

CMC good
1 cycle/ 8 weeks.

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
N/A

Date____________
Initials________

RLD = Solu Medrol for Injection 1 gram (base)/vial
Pharmacia + Upjohn Co. NDA 11-856 (006)

6. Vacant
Deputy Dir., DLPS

Date____________
Initials________

7. Peter Rickman
Director, DLPS
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 8/3/04 (verified 8/12/04). No OAI alerts noted. Bio waiver granted under 21 CFR 320.24(b)(6). The change in ingredients for the buffer is allowed under 314.94(a)(9)(iii). Office-level bio endorsed 8/4/04. Microbiology/sterility assurance endorsed 8/9/04. FPL found acceptable for approval 8/12/04. CMC found acceptable for approval 8/12/04. Methods validation is not required - compendial.

Date 8/12/04
Initials [signature] for

8. Robert L. West
Deputy Director, OGD
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments: There are no unexpired patents or exclusivity currently listed in the Orange Book for this drug product. This ANDA was granted "Expedited Review" status by the Center Director as a medically necessary drug product. This ANDA was approved in one-cycle (57-days).
This ANDA is recommended for final approval.

Date 8/12/2004
Initials Robert L. West

9. Gary Buehler
Director, OGD
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

Date 8/11/04
Initials GB

10. Project Manager, **Wanda Pamphile**
Team 5
Review Support Branch

Date 04-AUG-12
Initials WP

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
4:16 Time notified of approval by phone 4:20 Time approval letter faxed
FDA Notification:
8/12/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/12/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-612

CORRESPONDENCE

AMERICAN PHARMACEUTICAL PARTNERS, INC.

505(j)(2)(A)

June 16, 2004

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: Methylprednisolone Sodium Succinate for Injection, USP
1-g Multiple Dose Vial (Product Code 276530)
Manufacturing Site: Melrose Park, Illinois
7 Volumes

ORIGINAL ANDA

EXPEDITED REVIEW REQUESTED

Dear Mr. Buehler,

This Abbreviated New Drug Application (ANDA) is submitted in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Methylprednisolone Sodium Succinate for Injection, USP 1-g multiple dose vial. The reference listed drug, Solu-Medrol®, was manufactured by Pfizer (previously Pharmacia & Upjohn), however per FDA's drug shortage list, Pfizer is no longer able to produce the drug. Since FDA has determined that the drug product is medically necessary, American Pharmaceutical Partners requests expedited review of this ANDA for Methylprednisolone Sodium Succinate for Injection, USP.

American Pharmaceutical Partners, Inc. will manufacture this product in its manufacturing facility located at 2020 Ruby Street, Melrose Park, Illinois 60160. This ANDA contains all the information required to describe the chemistry, manufacturing and control of Methylprednisolone Sodium Succinate for Injection, USP 1-g multiple dose vial. This application, also, contains a request for the waiver of *in vivo* bioequivalence studies. The product is manufactured using ——————— and, therefore, contains microbiology and sterility assurance information (Section XXII).

RECEIVED
JUN 17 2004
OGD/CDER

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

The application has been formatted according to the information in the *Guidance for Industry: Organization of an ANDA*, dated February 1999. An Executive Summary explaining the organization of this application follows this cover letter. The ANDA consists of seven volumes.

American Pharmaceutical Partners Inc. is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the application, and a technical review copy (in a red folder) that contains all of the information in the archival copy. Three copies of the analytical methods validation section are included in red folders. One set of the draft labeling is included in the archival copy of this ANDA, and four sets of the draft labeling are included in the review copy. A separate copy of the bioequivalence section is provided in an orange folder. The bioequivalence section consists of a request for a waiver from the need to conduct a bioequivalence study and includes a copy of sections I through V for the reviewer's convenience.

Per the final rule on FDA Docket No. 2000N-1652, *Requirements for Submission of labeling for Human Prescription Drugs and Biologics in Electronic Format*, an electronic copy of the package insert is being sent to FDA at 7500 Standish Place, E-150, Rockville, MD 20855.

In compliance with 21 CFR 314.94(d)(5), a field copy of this ANDA is being provided to the director of the Chicago District Office of the Food and Drug Administration. We certify that the field copy is a true and complete copy of this application.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(708) 486-2024** or Dale Carlson, Associate Director of Regulatory Affairs, at **(708) 486-2071.**

Sincerely,

Kathleen Dungan

Kathleen Dungan
Senior Regulatory Scientist

ANDA 40-612

American Pharmaceutical Partners, Inc.
Attention: Kathleen Dungan
2045 North Cornell Avenue
Melrose Park, IL 60160

JUN 28 2004

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial

DATE OF APPLICATION: June 16, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 17, 2004

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

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

Should you have questions concerning this application, contact:

Wanda Pamphile
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

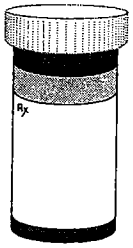
ANDA 40-612

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/MShimer,Chief,RSB _____ date 29-Jun 2004
HFD-615/ACamphire,CSO _____ date 25-Jun-2004
Word File V:\Firmsam\APP\ltrs&rev\40612.ACK
F/T June 25, 2004 AC
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Kathleen Dungan
APP
Fax: 708-343-4269 **Phone:** 708-486-2024

From: Ruby Wu
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 2 **Date:** July 26, 2004

Comments:

Labeling comments provided for ANDA 40-612 Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	40-612
Date of Submission:	June 16, 2004
Applicant's Name:	American Pharmaceutical Partners, Inc.
Established Name:	Methylprednisolone Sodium Succinate for Injection USP, 1 g/vial

---

Labeling Deficiencies:

1. CONTAINER (1 g/vial [16 mL when mixed])
   a. Add "Recommended Diluent Contains Benzyl Alcohol as a Preservative" to the principal display panel to be consistent with the RLD.
   b. Revise "16 mL Multiple Dose vial" to read:

      "8-125 mg doses
      One Multiple dose Vial"

2. CARTON (1 vial)
   a. Refer to CONTAINER comments 1.a. and 1.b.
   b. Back Panel: "...16 mL Bacteriostatic Water..." [correct spelling of "Bacteriostatic"]
   c. Side Panel: "Use within 48 hours after mixing"

3. PROFESSIONAL INSERT
   a. DESCRIPTION
      i. Fourth paragraph: "...1 gram vial for..."
      ii. Sixth paragraph: "...the tonicity for the 1 g per 16 mL solution is 0.40 osmolar...."
   b. HOW SUPPLIED: "...1 g/vial (16 mL when mixed), multiple dose vial..."

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

http://www.fda.gov/cder/guidance/5004fnl.htm.

Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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.

John J Grunford

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AMERICAN PHARMACEUTICAL PARTNERS, INC.

August 2, 2004

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ARCHIVAL

Re: ANDA #40-612
Methylprednisolone Sodium Succinate for Injection, USP
1-g Multiple Dose Vial (Product Code 276530)
Manufacturing Site: Melrose Park, Illinois

FAX MICROBIOLOGY AMENDMENT

ORIG AMENDMENT
NAS

Dear Mr. Buehler,

Reference is made to our June 16, 2004 submission of Abbreviated New Drug Application (ANDA) #40-612 for Methylprednisolone Sodium Succinate for Injection, USP. Reference is, also, made to the July 26, 2004 telephone communication from Nrapendra Nath, OGD, FDA, to Kathleen Dungan, APP, in which Dr. Nath requests preservative effectiveness test data for the drug product with the diluent, in order to support the labeling.

Provided in **Attachment 1** are copies of the preservative effectiveness test method validation report and the test results. The results support product labeling.

In compliance with 21 CFR § 314.96(b), a true and complete copy of this amendment is being submitted concurrently to the Chicago Distirct Office.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(708) 486-2024**, or Dale Carlson, Associate Director of Regulatory Affairs, at **(708) 486-2071**.

Sincerely,

Kathleen Dungan

Kathleen Dungan
Senior Regulatory Scientist

RECEIVED
AUG 0 3 2004
OGD / CDER

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1092

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com

AMERICAN PHARMACEUTICAL PARTNERS, INC.

N/A F
ORIG AMENDMENT
ARCHIVAL

August 05, 2004

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA #40-612
Methylprednisolone Sodium Succinate for Injection, USP
1-g Multiple Dose Vial (Product Code 276530)
Manufacturing Site: Melrose Park, Illinois

LABELING AMENDMENT

Dear Mr. Buehler,

Reference is made to our June 16, 2004 submission of Abbreviated New Drug Application (ANDA) #40-612 for Methylprednisolone Sodium Succinate for Injection, USP. Reference is, also, made to the enclosed labeling deficiency letter from Ruby Wu, FDA, to Kathleen Dungan, APP, dated July 26, 2004.

American Pharmaceutical Partners, Inc. is submitting this amendment in response to the comments made in the above-referenced letter. For ease of review, the reviewer's observations are provided in bold, followed by APP's response.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(708) 486-2024**, or Dale Carlson, Associate Director of Regulatory Affairs, at **(708) 486-2071**.

Sincerely,

Kathleen Dungan

Kathleen Dungan
Senior Regulatory Scientist

RECEIVED
AUG 06 2004
OGD / CDER

2045 NORTH CORNELL AVENUE
MELROSE PARK, IL 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 486-2095
www.appdrugs.com