CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 40-583

Name: Methylprednisolone Sodium Succinate for Injection USP, 40 mg (base)/vial and 125 mg (base)/vial

Sponsor: American Pharmaceutical Partners, Inc.

Approval Date: July 30, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-583

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APPLICATION NUMBER:

ANDA 40-583

APPROVAL LETTER

ANDA 40-583

JUL 30 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 February 25, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Methylprednisolone Sodium Succinate for Injection USP, 40 mg (base)/vial and 125 mg (base)/vial.

Reference is also made to your amendments dated April 30, May 18, June 30, and July 30, 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, 40 mg (base)/vial and 125 mg (base)/vial, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Solu-Medrol® for Injection, 40 mg (base)/vial and 125 mg (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,

Robert Lumpkin for 1/30/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-583
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-647/S.Patankar 7/27/04
HFD-645/S.Liu S.H. Liu 7/27/04
HFD-617/W.Pamphile WP 7/27/04
HFD-613/R.Wu RWu 7/26/04
HFD-613/J.Grace 7/27/2004
HFD-600/D.Obenhuber 7/27/04
HFD-600/N.Sweeney N. Sweeney 7.27.04

V:\FIRMSAM\APP\LTRS & REV\40583.AP.DOC

7/28/04
PAC'ed
EES for NDS is pending

APPROVAL

Robert Rudolph
7/28/04
Pending resolution of the following 2 EES ISSUES:
1. Current "OAI" alert in EES for the 2020 Ruby Street drug product manufacturing site
2 Pending (unscheduled) inspection of API supplier

7/30/04
EES is resolved.
RWW.
OK to approve.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-583

LABELING

AMERICAN PHARMACEUTICAL PARTNERS, INC.

451006/Issued: April 2004

METHYLPREDNISOLONE SODIUM SUCCINATE
FOR INJECTION, USP

For Intravenous or Intramuscular Administration

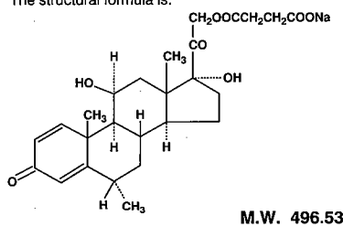
Rx only

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 two strengths for intravenous or intramuscular administration.

40 mg (Single Dose Vial) Each mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone; also, 1.6 mg monobasic sodium phosphate anhydrous; 17.46 mg dibasic sodium phosphate dried; 25 mg lactose hydrous; and benzyl alcohol.

125 mg (Single Dose Vial) Each 2 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone; also, 1.6 mg monobasic sodium phosphate anhydrous; 17.4 mg dibasic sodium phosphate dried; and benzyl alcohol.

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 tonicities are, for the 40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL, 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 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 antituberculous 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 40 mg single dose vial and the 125 mg single 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 40 mg/vial product with 1 mL of Bacteriostatic Water for Injection with Benzyl Alcohol, or reconstitute the 125 mg/vial product with 2 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.

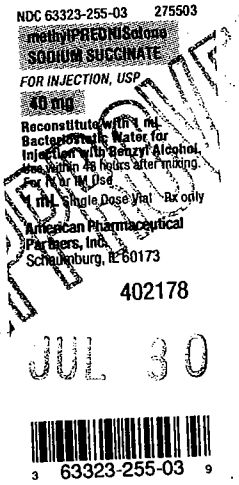
HOW SUPPLIED:

Product No.	NDC No.	
275503	63323-255-03	Methylprednisolone Sodium Succinate for Injection USP, 40 mg/vial, 1 mL single dose vial, in packages of 25.
275803	63323-258-03	Methylprednisolone Sodium Succinate for Injection USP, 125 mg/vial, 2 mL single dose vial, in packages of 25.

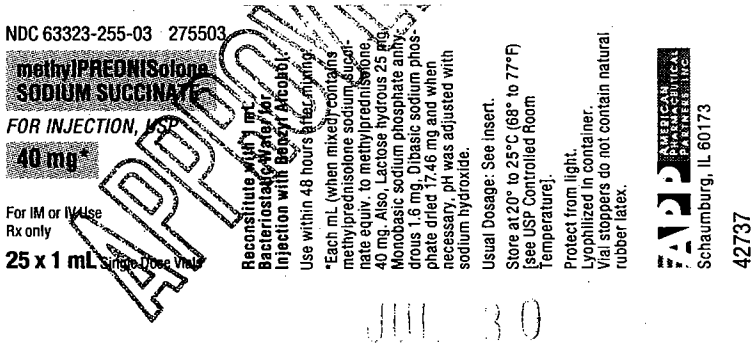
Vial stoppers do not contain natural rubber latex.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Schaumburg, IL 60173
451006
Issued: April 2004

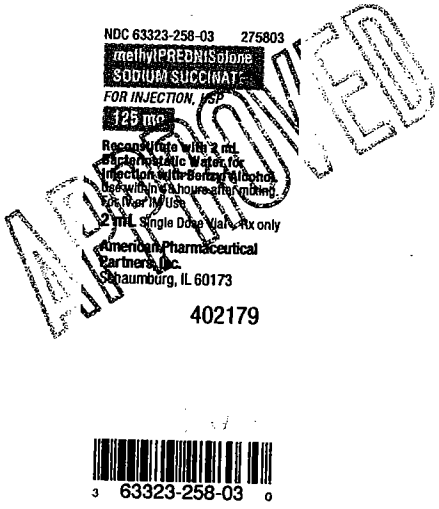
40-mg Product



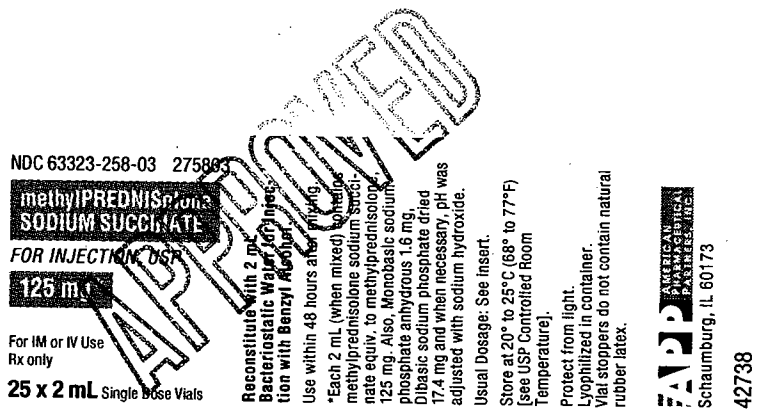
FOR LEGIBILITY ENLARGED TO 150% BY FDA STAFF



125-mg Product



FOR LEGIBILITY, ENLARGED TO 150% BY FOI STAFF



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-583

LABELING REVIEWS

1.1

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

ANDA Number: 40-583
Date of Submission: February 25, 2004
Applicant's Name: American Pharmaceutical Partners, Inc.
Established Name: Methylprednisolone Sodium Succinate for Injection USP, 40 mg/vial and 125 mg/vial

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Labeling Deficiencies

1. CONTAINER [40 mg/vial[(1 mL when mixed) and 125 mg/vial (2 mL when mixed)]
   a. Revise the "Reconstitute" statement to read: "**Reconstitute with XX mL Bacteriostatic Water for Injection with Benzyl Alcohol**. Use within 48 hours after mixing."
   b. To save space, you may elect to delete "See package insert for complete product information".
   c. Revise the "*Each XX mL contains" statement to read: "*Each XX mL (when mixed) contains..."
2. TRAY LABELING (25 X 1 mL or 2 mL vials)
   a. Principal display panel: "25 x XX mL Single Dose Vials"
   b. Revise the storage recommendation to read: "Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]"
   c. 125 mg/vial only: "...Dibasic sodium phosphate dried 17.4 mg and..."
   d. Refer to comments 1.a. and 1.c.
3. INSERT: Please refer to the attached mocked-up copy of your insert labeling for guidance.
   a. WARNINGS- Add the following as the sixth paragraph: "**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.**"
   b. PRECAUTIONS- "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."
   c. HOW SUPPLIED: Refer to comment 2.b.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

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.

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

Attachment: Mocked-up copy of your insert labeling

13 pages of draft labeling have been removed from this portion of the document.

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?

Package insert, DESCRIPTION section: Please verify that the inactive ingredients list for the 125 mg/vial product and the following information in the last paragraph "...40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL, 0.40 osmolar..." are accurate.

FOR THE RECORD:

GRANTED EXPEDITED REVIEW

1. MODEL LABELING -
   The RLD is Solu-Medro® (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. APP does not provide, but states in labeling that reconstitute with Bact. Water with Benzyl Alcohol. Ok, firm does not have to provide Benzyl Alcohol."
   - USP: Packaging and storage-
     Preserve in Containers for Sterile Solids as described under Injections

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.	N/A	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

[Vol. B1.1, pg. 13]

3. MANUFACTURING FACILITY (Vol. B1.1, pg. 220)
   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	40 mg/vial (1 mL constituted solution) [Vol B1.1, pg. 91] Composition per mL	125 mg/vial (2 mL constituted solution) [Vol B1.1, pg. 88] Composition per 2 mL
Methylprednisolone	(eq 40 mg methylprednisolone)	eq 125 mg) [pg. 88]
Monobasic Sodium	1.84 (eq 1.6 mg anhydrous monobasic sodium phosphate)	1.6 mg
Dibasic Sodium Phosphate	32.97 mg (eq 17.46 mg anhydrous dibasic sodium phosphate)	17.4 mg
Lactose monohydrate	25 mg	-----
Sodium Hydroxide	q.s. to adjust pH	q.s. to adjust pH
Water for injection	q.s. to 1 mL	q.s. to 1 mL

The active ingredient is [Vol. B1.1, pg. 6]

7. PRODUCT LINE:
   RLD- 40 mg Act-O-Vial System (Single-Dose Vial)
   1 mL NDC 0009-0113-12
   25 x 1 mL NDC 0009-0113-19
   125 mg Act-O-Vial System (Single-Dose Vial)
   2 mL NDC 0009-0190-09
   25 x 2 mL NDC 0009-0190-16
   RLD also marketed in other strengths

   ANDA- 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. B1.4, pg. 985)
   Vial: USP type I flint, tubing, glass vials
   Stopper: gray
   Seal: flip cap, aluminum crimp
   The filled, stoppered, capped and labeled vials are then placed into paperboard, lidded trays
   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 3-mL flint vial [Vol B1.4, pg. 1069]

10. BIOEQUIVALENCE: Pending as of 4/5/04

Date of Review: April 7, 2004 Date of Submission: February 25, 2004

Primary Reviewer: Ruby Wu Date: 4/7/04

Team Leader: John Grace Date: 4/7/04

cc: ANDA: 40-583
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
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Review

Expedited Review ANDA

APPROVAL SUMMARY

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

ANDA Number: 40-583
Date of Submission: May 18, 2004 (Amendment-FPL)
Applicant's Name: American Pharmaceutical Partners, Inc.
Established Name: Methylprednisolone Sodium Succinate for Injection USP, 40 mg/vial and 125 mg/vial

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER [40 mg/vial[(1 mL when mixed) and 125 mg/vial (2 mL when mixed)]
Satisfactory in final print as of the May 18, 2004 submission. [Vol. 2.1]

TRAY LABELING (25 X 1 mL or 2 mL vials)
Satisfactory in final print as of the May 18, 2004 submission. [Vol. 2.1]

Professional Package INSERT:
Satisfactory in final print as of the May 18, 2004 submission. [Vol. 2.1; issued April 2004]

Revisions needed post-tentative approval: Yes.
The following are requested insert labeling revisions from my review of your amendment dated May 18, 2004 for ANDA 40-583 for Methylprednisolone Sodium Succinate for Injection USP, 40 mg/vial and 125 mg/vial. The revisions are "**POST-APPROVAL**" revisions and may be submitted in an annual report, provided the changes are described in full.

1. INDICATIONS AND USAGE, Endocrine Disorders, second paragraph: "...drug of choice; mineralocorticoid...synthetic analogs are used)" [add semicolon and "analogs"]
2. ADVERSE REACTIONS, Neurological: "...papilledema (Pseudo-tumor..."

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.

PATENT AND EXCLUSIVITY:

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.	N/A	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

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?

Response : [redacted] *. It is satisfactory*

Package insert, DESCRIPTION section: Please verify that the inactive ingredients list for the 125 mg/vial product and the following information in the last paragraph "...40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL, 0.40 osmolar..." are accurate.

Response : *The osmolarity on the Package Insert is accurate.*

Is the product light sensitive?

Response: *Here is the response to your question regarding light sensitivity and amber containers for ANDA # 40583, Methylprednisolone Sodium Succinate for injection, 40 mg/vial and 125 mg/vial.*

1. Methyl Prednisolone Sodium Succinate for Injection has a USP monograph which does not state " Preserve in light-resistant containers".

2. [redacted] *also does not provide requirement for saving in light-resistant containers.*

3. Methylprednisolone Sodium Succinate monograph specifies storage in light-resistant containers.

4. Currently the firm is using Flint glass Type I.

5. I checked in PDR and the Solu-Medrol (RLD) did not state that they supply the product in amber vials. If RLD is not sold in amber vials I do not see a requirement for amber vials.

6. The drug substance may be less stable after reconstitution. Most of the lyophilazation vials I have seen are clear. So if you are going to request that the firm use amber vials please let me know. This means they would have to rework and resubmit the material.

7. This ANDA is expedited due to paucity of the material.

8. We have already mailed the letter with CMC deficiencies.

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. APP does not provide, but states in labeling that reconstitute with Bact. Water with Benzyl Alcohol. Ok, firm does not have to provide Benzyl Alcohol."
   - USP: Packaging and storage-Preserve in Containers for Sterile Solids as described under Injections

2. PATENTS AND EXCLUSIVITIES [Vol. B1.1, pg. 13]

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.	N/A	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. B1.1, pg. 220)
   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	40 mg/vial (1 mL constituted solution) [Vol B1.1, pg. 91] Composition per mL	125 mg/vial (2 mL constituted solution) [Vol B1.1, pg. 88] Composition per 2 mL
Methylprednisolone	(eq 40 mg methylprednisolone)	(eq 125 mg) [pg. 88]
Monobasic Sodium	1.84 (eq 1.6 mg anhydrous monobasic sodium phosphate)	1.6 mg
Dibasic Sodium Phosphate	32.97 mg (eq 17.46 mg anhydrous dibasic sodium phosphate)	17.4 mg
Lactose monohydrate	25 mg	
Sodium Hydroxide	q.s. to adjust pH	q.s. to adjust pH
Water for injection	q.s. to 1 mL	q.s. to 1 mL

The active ingredient is [Vol. B1.1, pg. 6]

7. PRODUCT LINE:
   RLD- 40 mg Act-O-Vial System (Single-Dose Vial)
   1 mL NDC 0009-0113-12
   25 x 1 mL NDC 0009-0113-19
   125 mg Act-O-Vial System (Single-Dose Vial)
   2 mL NDC 0009-0190-09
   25 x 2 mL NDC 0009-0190-16
   RLD also marketed in other strengths

   ANDA- 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. B1.4, pg. 985)
   Vial: USP type I flint, tubing, glass vials (product not light sensitive-see Note to the chemist)
   Stopper: gray
   Seal: flip cap, aluminum crimp
   The filled, stoppered, capped and labeled vials are then placed into paperboard, lidded trays
   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 3-mL flint vial [Vol B1.4, pg. 1069]

10. BIOEQUIVALENCE and MICROBIOLOGY:Acceptable [per MQ note]

Date of Review: June 1, 2004 Date of Submission: May 18, 2004

Primary Reviewer: Ruby Wu Date: 6/1/04

Team Leader: John Grace Date: 6/3/04

cc: ANDA: 40-583
DUP/DIVISION FILE
HFD-613/Rwu/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-583

CHEMISTRY REVIEWS

ANDA 40-583

Methylprednisolone Sodium Succinate For Injection USP, 40 mg/vial and 125 mg/vial

American Pharmaceutical Partners, Inc.

Suhas Patankar, Ph.D.
Chemistry Division I