CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
014901Orig1s043

Trade Name: KENALOG®-40 INJECTION

Generic or Proper Name: triamcinolone acetonide injectable suspension, USP

Sponsor: Bristol-Myers Squibb Company

Approval Date: 10/23/2015

Indication:

INTRAMUSCULAR
Where oral therapy is not feasible, injectable corticosteroid therapy, including Kenalog-40 Injection (triamcinolone acetonide injectable suspension, USP) is indicated **for intramuscular use** as follows:
Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.
Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).
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), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.
Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.
Hematologic disorders: Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

INDICATIONS (continued from prior page):

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.
Neoplastic diseases: For the palliative management of leukemias and lymphomas.
Nervous system: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.
Ophthalmic diseases: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.
Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.
INTRA-ARTICULAR
The intra-articular or soft tissue administration of Kenalog-40 Injection is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epidondylitis, rheumatoid arthritis, synovitis, or osteoarthritis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

014901Orig1s043

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**x**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

014901Orig1s043

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 14901/S-043

APPROVAL LETTER

Bristol-Myers Squibb Company
Attention: Jennifer Mahilo, Associate Director,
Global Regulatory Sciences - CMC
311 Pennington-Rocky Hill Road
Bldg# 19, Rm# 362
Pennington, NJ 08534

Dear Ms. Mahilo:

Please refer to your Supplemental New Drug Application (sNDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kenalog-40® Injection (triamcinolone acetonide injectable suspension, USP).

This "Prior Approval" supplemental new drug application provides for the harmonization of the drug product formulation, release specification, and packaging globally.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

Ramesh Raghavachari -S

Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2015.10.23 22:34:06 -04'00'

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

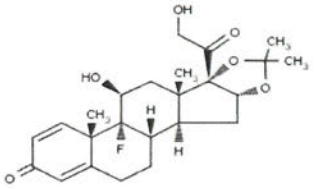
APPLICATION NUMBER:

014901Orig1s043

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION Branch 1/DPMA1/OLDP/OPQ	2. NDA NUMBERS 014901
3. NAME AND ADDRESS OF APPLICANT Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Tel: (609) 818-5857, Fax: (609) 818-5831 Jennifer T. Mahilo, Associate Director, Global Regulatory Sciences – CMC jennifer.mahilo@bms.com		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) & DATES(S) **S-043; PAS; SDN 144** Letter Date: 6/30/15 Stamp Date: 6/30/15 **Due Date: 10/30/15**
6. NAME OF DRUG Kenalog 40	7. NONPROPRIETARY NAME Triamcinolone Acetonide Injection	

8. SUPPLEMENT PROVIDES FOR: CMC Prior Approval Supplement - Harmonization of drug product formula, specifications, and packaging

9. PHARMACOLOGICAL CATEGORY Treatment of joint inflammation/various dermatologic conditions	10. HOW DISPENSED RX x OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 40 mg/mL	
14. CHEMICAL NAME AND STRUCTURE 9-Fluoro-11 β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20dione cyclic 16, 17-acetal  MW 434.50		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO

16. COMMENTS: Applicant's intention to update the formula, specifically the excipient composition, of the injectable suspension in order to harmonize the formula that is marketed globally is acceptable.
Drug product specification and packaging changes are also acceptable.

17. CONCLUSION AND RECOMMENDATION
Chemist recommends approval of this supplement.

18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED October 8, 2015

Background

The purpose of this submission is to update the formula, specifically the excipient composition, of the injectable suspension in order to harmonize the formula that is marketed globally. Additionally, minor drug product specification and packaging changes are included.

The below changes are included in this submission:

1. Formulation: A minor change in the excipient quantity levels for Benzyl Alcohol, Sodium Chloride, Sodium Carboxylethylcellulose, Sodium Hydroxide and Hydrochloric Acid.

2. Release Specification: Change from [redacted] (b) (4) for Triamcinolone Acetonide Identification. [redacted] (b) (4), a USP method, is approved for determination of Assay, Impurities and Uniformity of Dosage Units.

3. Packaging: Change in the [redacted] (b) (4) cap seal [redacted] (b) (4) for both the 1 mL vial (utilizes a [redacted] (b) (4)) and 5 mL vial presentations.

Review:

2.3 Quality Overall Summary

INTRODUCTION

Triamcinolone acetonide injectable suspension, USP 40 mg/mL (Kenalog 40) is a synthetic corticosteroid with an anti-inflammatory action. The drug product is a sterile, aqueous suspension marketed in three different presentations: 1 mL, 5 mL and 10 mL vials, all providing a 40 mg/mL concentration of triamcinolone acetonide. Manufacturing, primary and secondary packaging, quality control testing and batch release is currently conducted at the Bristol-Myers Squibb (BMS) site in Anagni, Italy.

The proposed changes to the formula are outlined in Table 1 below.

Table 1: Composition of Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Component	Reference	Function	Current quantity per mL (mg)	Proposed quantity per mL (mg)
Triamcinolone Acetonide	USP	Active Pharmaceutical Ingredient	40	40
Benzyl Alcohol	(b) (4)	Preservative Agent	(b) (4)	(b) (4)
Sodium Chloride		Isotonic Agent		
Polysorbate 80		(b) (4)		
Sodium Carboxymethylcellulose		(b) (4)		
Sodium Hydroxide		pH Adjuster		
Hydrochloric Acid		pH Adjuster		
(b) (4)				

Evaluation: ***Acceptable***

Applicant states that the proposed range for excipient addition is comparable to that of the drug product formula marketed in Spain, France, Netherlands and European Nordic Countries. Stability data for above mentioned formulation (i.e. reflecting the potential proposed formulation) versus the current formula has been provided in Module 3.2.P.8 "Stability".

The viscosity of the vehicle guarantees that the active ingredient remains in suspension. As the final vehicle viscosity (b) (4) limit of (b) (4) will remain unchanged, there is no impact on the quality, efficacy and safety of the drug product.

Viscosity (b) (4) results for three (3) batches of current formula and three (3) batches of proposed formula showing that no change occur in the final vehicle viscosity are reported in Table 2.

Table 2: Viscosity (b) (4) results for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Current Formula		Proposed Formula	
Batch No	Viscosity (b) (4)	Batch No	Viscosity (b) (4)
4D80514		3K77190	
4A82692		4B78385	
4F77756		4F80364	

The proposed changes to the batch formulation as based on the commercial batch sizes are

summarized in Table 3 below.

Table 3: Batch Formulation for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Component	Current Minimum Commercial Batch Size (b) (4) ( )	Proposed Minimum Commercial Batch Size (b) ( )	Current Minimum Commercial Batch Size (b) (4)	Proposed Minimum Commercial Batch Size (b) (4) ( )
Triamcinolone Acetonide	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Benzyl Alcohol[a]				
Sodium Chloride[a]				
Polysorbate 80[a]				
Sodium Carboxymethylcellulose[a]				
Sodium Hydroxide				
Hydrochloric Acid				
(b) (4)[a]				
(b) (4)				

The following minor changes are also presented in this PAS:

1. Release specification:
   Triamcinolone Acetonide Identification by (b) (4) will be replaced by (b) (4) and (b) (4) methods.

Evaluation: ***Acceptable***

These methods are already approved as Assay and Impurities tests.

2. Primary and secondary packaging components
   Cap seal for (b) (4): The color of the cap is being changed from (b) (4).
   Cap seal for 5ml vial: The color of the cap seal is being changed from (b) (4).

These changes are summarized in Tables 4 and 5 below.

Table 4: Specifications for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Test	Current Acceptance Criteria	Proposed Acceptance Criteria
Description	White (b) (4)	White (b) (4)
Identity	(b) (4)	(b) (4)
Identity - (b) (4)		
Identity- (b) (4)		
pH	5.0 - 7.5	5.0 - 7.5
Benzyl Alcohol (b) ( )	(b) (4)	(b) (4)
Uniformity of Dosage Unit	(b) (4)	(b) (4)
Cleanliness	(b) (4)	(b) (4)
Particle Size - Microscopic		
Triamcinolone Acetonide Assay		
Net Contents- 1 mL: Avg		
Net Contents- 5 mL: Avg		
Net Contents- 10 mL: Avg		
Impurities/degradants: Individual Unknown Individual known Total		
Sterility - Direct		
(b) (4)		

Table 5: Packaging Components for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

	Component	Current Description	Proposed Description
1 mL vial presentation	vial stopper seal	(b) (4)	
5 mL vial presentation	vial stopper seal		
10 mL vial presentation	vial stopper seal		

Evaluation: ***Acceptable***

The changes do not cause any adverse effect to the drug product quality.

3.2.P Drug Product

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Triamcinolone acetonide injectable suspension, USP 40 mg/mL is a syntetic glucocorticoid corticosteroid is a synthetic glucocorticoid corticosteroid with anti-inflammatory action, containing 40 mg/mL of triamcinolone acetonide as active substance. Triamcinolone acetonide injectable suspension, USP 40 mg/mL, is marketed in 1, 5 and 10 mL presentations. These presentations are packaged, respectively, in (b) (4) 5, and 10 mL (b) (4) glass vials with (b) (4) stoppers and (b) (4) seals, and inserted into printed cardboard boxes.

The unit composition of triamcinolone acetonide injectable suspension, USP 40 mg/mL, including the quality and function of each component, is provided in Table 3.2.P.1-1.

Table 3.2.P.1-1: Unit Composition of Triancinolone acetonide injectable suspension, USP 40 mg/mL

Component	Quality Standard	Function	Quantity per mL (mg)
Triamcinolone Acetonide	USP	Active Pharmaceutical Ingredient	40
Benzyl Alcohol	(b) (4)	Preservative Agent	(b) (4)
Sodium Chloride		Isotonic Agent	
Polysorbate 80		(b) (4)	
Sodium Carboxymethylcellulose		(b) (4)	
Sodium Hydroxide		pH Adjuster	
Hydrochloric Acid		pH Adjuster	
(b) (4)		(b) (4)	(b) (4)

3.2.P.3.2 Batch Formula

A representative batch formula for the drug product, for a typical batch size of (b) (4) of triamcinolone acetonide injectable suspension, USP 40 mg/mL, manufactured at the Bristol-Myers Squibb, Anagni facility, is provided in Table 3.2.P.3.2-1.

Table -1: Batch Formulation for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/ml

Component	Minimum Commercial Batch Size (b) (4)	Maximun Commercial Batch Size (b) (4)
Triamcinolone Acetonide	(b) (4)	(b) (4)
Benzyl Alcohol[a]		
Sodium Chloride[a]		
Polysorbate 80[a]		
Sodium Carboxymethylcellulose[a]		
Sodium Hydroxide		
Hydrochloric Acid		
(b) (4) [a]		

[a] (b) (4)

Specific weight of vehicle: (b) (4)
Specific weight of suspension: (b) (4)

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specifications

Specifications for triamcinolone acetonide injectable suspension, 40 mg/mL, are presented in Table 3.2.P.5.1-1. The "G" or "S" suffix which follows each analytical method number denotes whether the method is a general method or specific method, respectively. The description of analytical procedures is reported in detail in section 3.2.P.5.2 *"Analytical Procedures"*.

Table 3.2.P.5.1-1: Specifications for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Test Description	Acceptance Criteria	Analytical Procedure
Description	White (b) (4)	(b) (4)
Identity - (b) (4)	(b) (4)	
Identity - (b) (4)		
Identity- (b) (4)		
pH	5.0 - 7.5	
Benzyl Alcohol - (b) (4)	(b) (4)	
Uniformity of Dosage Unit		
Cleanliness		
Particle Size (b) (4)		
Triamcinolone Acetonide Assay - (b) (4)		
Net Contents- 1 mL: Avg		
Net Contents- 5 mL: Avg		
Net Contents- 10 mL: Avg		

Table 3.2.P.5.1-1: Specifications for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Test Description	Acceptance Criteria	Analytical Procedure
Impurities/degradants: Individual Unknown Individual known Total Sterility - Direct (b) (4)	(b) (4)	(b) (4)
(b) (4)		

3.2.P.7 CONTAINER CLOSURE SYSTEM

Triamcinolone acetonide injectable suspension, USP 40 mg/mL is marketed in the following presentations: 1 mL, 5 mL and 10 mL stoppered/sealed vials.

3.2.P.7.1 Primary Packaging Components

Information regarding the primary components for triamcinolone acetonide injectable suspension, USP 40 mg/mL, including the respective materials of construction, is provided in Table 3.2.P.7.1-1.

Components with minor changes are in bold.

Table 3.2.P.7.1-1: Primary Packaging Components for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Component	Description
Vial	(b) (4)
Vial	
Vial	
Stopper	
Stopper	
Seal	
Seal	

3.2.P.7.1.1 Packaging Components Specifications

Table 3.2.P.7.1.1.-1 summarizes the marketing package configuration and identifies the primary packaging component for triamcinolone acetonide, injectable suspension, USP 40 mg/mL.

Table 3.2.P.7.1.1-1: Packaging Material Specifications for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL

Attribute	Value
Style Finish Drawing Glass Type	(b) (4)
Style Finish Drawing Glass Type	
Style Finish Drawing Glass Type	
Style Finish Drawing (b) (4)	
Style Finish Drawing (b) (4)	
Style Finish Drawing Materials	
Style Finish Drawing Materials	

The drawing of (b) (4) seal is provided.

3.2.P.8 STABILITY - PACKAGED BY ANAGNI, ITALY

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.1.1 Summary of Drug Product Stability Studies

Triamcinolone acetonide, injectable suspension, USP 40 mg/ml, is manufactured, packaged, and tested for stability by BMS in Anagni, Italy.

The market-life stability studies for triamcinolone acetonide, injectable suspension, USP 40 mg/ml, are conducted at long term storage conditions, 30°C/65% Relative Humidity [RH], throughout the shelf-life (b) (4) to support the recommended storage condition: "Store at controlled room temperature, 20°-25°C (68°-77°F), avoid freezing and protect from light. Do not refrigerate". Data is provided in Section 3.2.P.8.3 "*Stability Data*".

The stability data provided in this submission are for one batch of the suspension formulated as proposed, with the change in excipients formulation. For comparison, also provided is data for the current US registered formula. Data through shelf life is provided for both. Additionally, six months accelerated data is provided for the batch of product in the proposed formulation.

Based on the stability data presented in this submission, both formulations of triamcinolone acetonide injectable suspension, USP 40 mg/ml, exhibit excellent chemical and physical stability for at least 24 months when stored at 25°C/60% RH or 30°C/65% RH.

3.2.P.8.1.2 Batches Tested and Packaging

The batches are summarized in Table 3.2.P.8.1.2-1. The stability data for these batches are provided in section 3.2.P.8.3.

Table 3.2.P.8.1.2-1: Triamcinolone Acetonide Injectable Suspension, USP 40 mg/mL Stability Batches

Batch No.	Vial size	Formulation	Date of Manufactur.	Storage Condition	Months of Stability	Study Status
8J41084PJ	1 mL	Proposed	10/2008	30 °/65% RH	24	completed
8J41084PJ	1 mL	Proposed	10/2008	40 °/75% RH	6	completed
0C66873	1 mL	Current	03/2010	30 °/65% RH	24	completed

3.2.P.8.3.2 Summary Data Tables

Stability data for the batches provided in Table 3.2.P.8.1-1 is provided on Tables 3.2.P.8.3.2-1, 3.2.P.8.3.2-2 and 3.2.P.8.3.2-3.

Table 3.2.P.8.3.2-1: 30°C/65%RH Stability Data for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/ml, 1 mL, Batch 8J41084PJ

		Time Points (Months)				
Test	**Specifications**	**Initial**	**6**	**12**	**18**	**24**
Description	White (b) (4) (b) (4)	Complies	Complies	Complies	Complies	Complies
pH	5.0 - 7.5	6.3	6.2	6.3	6.2	6.2
Triamcinolone Acetonide Assay	(b) (4)					
Benzyl Alcohol						
Individual Impurities						
Total Impurities						
Sterility	Must be sterile	Sterile	NR	NR	NR	Sterile

Table 3.2.P.8.3.2-2: 40°C/75%RH Stability Data for Triamcinolone Acetonide Injectable Suspension, USP 40 mg/ml, 1 mL, Batch 8J41084PJ

		Time Points (Months)				
Test	**Specifications**	**Initial**	**1**	**2**	**3**	**6**
Description	White (b) (4) (b) (4)	Complies	Complies	Complies	Complies	Complies
pH	5.0 - 7.5	6.3	6.0	6.1	6.2	6.2
Triamcinolone Acetonide Assay	(b) (4)					
Benzyl Alcohol						
Individual Impurities						
Total Impurities						
Sterility	Must be sterile	Sterile	NR	NR	NR	Sterile

Table 3.2.P.8.3.2-3: 30°C/65%RH Stability Data Triamcinolone Acetonide Injectable Suspension, USP 40 mg/ml, 1 mL, Batch 0C66873

		Time Points (Months)				
Test	Specifications	Initial	6	12	18	24
Description	White (b) (4) (b) (4)	Complies	Complies	Complies	Complies	Complies
pH	5.0 - 7.5	5.7	5.7	5.8	5.8	5.8
Triamcinolone Acetonide Assay	(b) (4)					
Benzyl Alcohol						
Individual Impurities						
Total Impurities						
Sterility	Must be sterile	Sterile	NR	NR	NR	Sterile

Evaluation: ***Acceptable***

No trend was observed. Excellent stability has been demonstrated.

CONCLUSION AND RECOMMENDATION

Applicant's intention to update the formula, specifically the excipient composition, of the injectable suspension in order to harmonize the formula that is marketed globally is acceptable.

Drug product specification and packaging changes are acceptable.

Chemist recommends approval of this supplement.

Chongho Kim -S
Digitally signed by Chongho Kim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chongho Kim -S, 0.9.2342.19200300.100.1.1=1300085235
Date: 2015.10.14 10:47:06 -04'00'

Ramesh Raghavachari -S
Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2015.10.14 11:29:08 -04'00'