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RESEARCH**

APPLICATION NUMBER:

22-028

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

NDA#: 22-028
Sponsor: Sandoz Canada, Inc
Drug: Cosyntropin Injection
Indication: Diagnostic agent in the screening of patients with presumed adrenocortical insufficiency
Date of Submission: February 6, 2006
Primary Medical Reviewer: William Lubas, M.D., Ph.D.

I. Introduction and Background

Sandoz Canada, Inc. has submitted this 505(b)(2) new drug application for Cosyntropin Injection 0.25mg/mL seeking approval for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. The basis for approval is reliance on data from Cortrosyn (cosyntropin for injection), 0.25mg (NDA 16-750 approved in 1970, Amphastar Pharmaceuticals, Inc.); data from the literature supporting safety and efficacy; and study 50525, a single randomized, blinded, two-way, cross-over pharmacodynamic (PD) study. No PK or bridging toxicology studies were required for this new formulation as the sponsor was able to show a similar impurity profile to the reference product.

Current therapies available as a diagnostic agent in the screening for adrenocortical insufficiency include the listed drug relied upon, Cortrosyn.

II. Clinical Efficacy

Study 50525: This is a randomized, single dose, open-label, two-period, crossover bioequivalence study comparing the plasma cortisol response to Cosyntropin injection 0.25mg and Cortrosyn 0.25mg. The primary endpoint was plasma cortisol level.

Study population: Subjects enrolled in the study were healthy, age greater than 18 years with a body mass index of 19 to 30 kg/m².

Study treatments: Eligible subjects were randomized to receive a single dose of either Cosyntropin injection 0.25mg or Cortrosyn 0.25mg as in iv bolus over 2 minutes. After a 5 day wash-out period, each subject received a single dose of the other preparation, again as an i.v. bolus over 2 minutes.

Efficacy measures: Blood samples for laboratory assessment of the plasma cortisol level, were taken at 22 different time points, from Hour -1 to Hour 6. The AUC, Cmax and Tmax were reported both as corrected for baseline cortisol and uncorrected values.

Results:

Disposition: A total of 24 subjects (13 men and 11 women) were enrolled and 22 subjects (13 men and 9 women) completed the study. A 28 year-old woman elected to withdraw from the study for personal reasons prior to Period 2, and a 26 year-old woman was withdrawn from the study prior to Period 2 because of difficulty with blood draw sampling.

Demographics: The mean age of enrollees was 36 ± 11 years, with a range of 21 to 55 years. The mean weight was 70.5 ± 11.4 kg with a range of 52.0 – 88.6 kg. The mean BMI was 24.0 ± 2.1 kg/m², with a range from 20.1 – 28.4 kg/m².

Cortisol Levels: As noted in the table below AUC, Cmax and Tmax values corrected for baseline cortisol following Cosyntropin and Cortrosyn injection are similar.

Study 50525: Plasma Cortisol Levels		
mean (SD)	Cosyntropin (test)	Cortrosyn (listed)
Baseline Corrected Cortisol Levels, all subjects		
AUC _{0-t} (ng.h/mL)	470 (167)	481 (222)
AUC _{0-inf} (ng.h/mL)	481 (166)	504 (214)
C _{max} (ng/mL)	153 (39)	152 (51)
T _{max} (h)	2.31 (0.55)	2.27 (0.39)
K _{el} (h ⁻¹)	1.76 (0.86)	1.17 (0.39)
T _{1/2el} (h)	0.46 (0.16)	0.69 (0.40)

When evaluated in terms of bioequivalence based on the cortisol response, the criteria prespecified were confidence intervals between 80 to 125% for the 90% geometric of the ratio (cosyntropin/ cortrosyn) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}. As outlined in the table below, the upper bound of the 90% confidence interval for AUC_{0-t} exceeded 125%. Further evaluation of the data revealed that in one subject (subject 5), cortisol levels following cortrosyn (listed drug) injection were lower than baseline at the 10, 20, and 30 minute sampling times. This resulted in negative corrected cortisol values. With exclusion of this subject's aberrant results, the confidence intervals for all three parameters fall within the prespecified range and suggest the two agents are bioequivalent.

Study 50525: Plasma Cortisol Levels			
	AUC _{0-t}	AUC _{0-inf}	C _{max}
All subjects			
Ratio (%)	106.96	100.99	104.15
90% Geometric C.I. (%)	90.45 – 126.47	87.61 – 116.41	92.54 – 117.23
All Subjects, excluding Subject 5			
Ratio (%)	104.54	98.91	103.05
90% Geometric C.I. (%)	87.89 – 124.34	85.43 – 114.52	91.03 – 116.65

Clinical use of stimulation testing with cosyntropin is performed with cortisol levels drawn at baseline, 30 minutes and 60 minutes. Adrenal sufficiency is evidenced by a cortisol level greater than 18 mcg/dL or at least a 7 mcg/dL increase in cortisol over baseline. Study 50525 enrolled healthy subjects, as indicated by the normal baseline mean cortisol levels. For both diagnostic agents, the mean post-dose cortisol levels were above 18 mcg/dL at both 30 and 60 minutes. Use of ACTH analogs are known to have a priming effect on the adrenal gland. When evaluated by the time period of administration, mean cortisol levels post study drug injection were slightly higher during Period 2 for both agents.

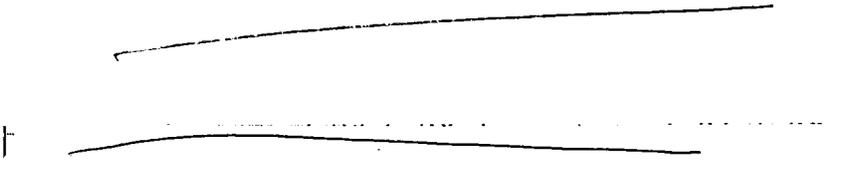
Study 50525: Plasma Cortisol Levels*		
mean (SD)	Cosyntropin (test)	Cortrosyn (listed)
Uncorrected Cortisol Levels, All Periods		
Baseline (mcg/dL)	13.2 (3.4)	12.9 (5.3)
C _{30min} (mcg/dL)	21.5 (2.6)	21.5 (2.9)
C _{60min} (mcg/dL)	25.0 (3.2)	24.7 (3.3)
Uncorrected Cortisol Levels, Period 1		
Baseline (mcg/dL)	13.2 (3.2)	14.5 (5.0)
C _{30min} (mcg/dL)	21.2 (2.3)	21.4 (2.9)
C _{60min} (mcg/dL)	24.9 (2.3)	24.4 (3.5)
Uncorrected Cortisol Levels, Period 2		
Baseline (mcg/dL)	13.3 (3.9)	11.6 (5.4)
C _{30min} (mcg/dL)	21.8 (3.1)	21.5 (3.0)
C _{60min} (mcg/dL)	25.2 (4.2)	25.0 (3.3)

*values have been converted from ng/mL to mcg/dL

While the mean cortisol levels for both study drugs reached the diagnostic thresholds for adrenal sufficiency, some subjects did not achieve adequate cortisol responses. As outlined in the table below, some subjects did not meet achieve a cortisol level of 18 mcg/dL or a change in cortisol levels greater than 7 mcg/dL at some point during the study. The most common abnormal response was a change in cortisol levels of less than 7 mcg/dL. However, in these subjects, the cortisol levels were above 18 mcg/dL and this would be considered adequate. Subject 22 did not achieve cortisol levels greater than 18 mcg/dl. However, there was a similar pattern with each agent.

Study 50525: Subjects with Suboptimal Cortisol Response								
subject	Period 1			Period 2				
	drug	0	30	60	drug	0	30	60

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Study 50525: Subjects with Suboptimal Cortisol Response								
subject	Period 1				Period 2			
	drug	0	30	60	drug	0	30	60
								
Study Drug A = cosyntropin (test), B = cortrosyn (listed)								

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Conclusions: When compared to the listed drug, cosyntropin's effect on cortisol is bioequivalent to cortrosyn. As evaluated, these two product elicited similar profiles of cortisol excursions from baseline. Cosyntropin will be efficacious for the evaluation of adrenocortical insufficiency.

III. Clinical Safety

Study 50525:

Disposition and exposure: Twenty two subjects received both doses of study drug during the trial. Two subjects withdrew after Period 1. Both received cortrosyn, the listed product during Period 1.

Deaths, serious adverse events, and adverse events leading to withdrawal: There were no deaths or serious adverse events during this study. No subjects withdrew from the study due to adverse events.

Adverse events: Overall, five subjects reported six adverse events prior to study drug administration and thirteen subjects experienced 24 adverse events following study drug administration. The occurrence of adverse events was even divided between the two study periods. Thirteen events were reported by subjects after administration of cosyntropin (test) while eleven events were reported by subjects following cortrosyn (listed drug).

One difference between the two diagnostic agents is the pH of the injected solution. While the listed drug cortrosyn is a buffered solution, the drug product for the test drug cosyntropin has an acidic pH (4.0). As outlined in Dr. Lubas's review, adverse events related to the site of administration were reported in 3 subjects following cosyntropin injection and one subject following cortrosyn injection. The findings were mild and self-limited. It is difficult to attribute these findings solely to the study drug versus related to the intravenous catheter placement. There was no clear evidence of study drug extravasation.

Laboratory evaluations: There were no clinically relevant changes noted for all chemistry and hematology parameters, except for one subject who developed a low hemoglobin and hematocrit during study Period 2. This was attributed to frequent phlebotomy required for the study.

Conclusions: There were no new safety signals noted in this small study. The pH of the cosyntropin preparation is acidic and does pose a theoretical risk of tissue injury if extravasation occurs. For this reason, the product should be labeled for intravenous use only and should not be given as an intramuscular injection.

I agree with Dr. Lubas' assessment that the immunogenicity profile of this preparation may be altered based on the pH of the product. However, this is a diagnostic agent that is not intended for long term therapy and therefore, the immunogenicity risk would be low. Should the company seek an indication for long term therapeutic uses, immunogenicity data will be required.

IV. Pharmacology/Toxicology

There are no new Pharmacology / Toxicology data submitted in this NDA. The impurity profile of cosyntropin was similar to the marketed product, cortrosyn. Therefore, preclinical bridging studies were not required.

V. Clinical Pharmacology

The single Clinical Pharmacology study submitted has been reviewed in the clinical section.

VI. CMC

As noted in Dr. Haber's review, there are two chemistry deficiencies that support an approvable action at this time. These deficiencies include:

- No bioassay data was submitted for either the drug substance or drug product to permit assessment of lot-to-lot bioactivity and comparison of product performance after manufacturing changes.
- There is insufficient data on drug impurities and degradation products to permit adequate stability testing and estimation of expiration dates for the product.

VII. Other Regulatory Requirements

VIIa. Financial Disclosure

Dr. Lubas has reviewed financial disclosure statements submitted by the applicant and all concerns have been adequately addressed.

VIIb. Pediatrics

No pediatric data is available for this product. As outlined by Dr. Lubas, the recommended dosage for testing in the pediatric population varies. While it may be beneficial to have efficacy and safety data in the pediatric population, this would be done in an attempt to unify the various dosing recommendations and not because of efficacy or

safety concerns. While the current cortrosyn label recommends half-dose for children under the age of 2 years, there is no evidence that a full dose of ACTH is harmful in the pediatric population.

VIIIc. Clinical Audits/Inspections

A DSI audit of the single clinical site was conducted for this submission. No clinical or analytical deficiencies were noted.

VIII. Conclusions and Recommendations

VIII.a. Conclusions

The clinical safety and efficacy profile of cosyntropin is comparable to that of cortrosyn in the adult population. From a clinical perspective, cosyntropin can be approved as a diagnostic agent in the screening for adrenocortical insufficiency. However, the chemistry deficiencies need to be addressed and therefore, the application is approvable. Pharmacodynamic data in the pediatric population would be beneficial although there are no clear reasons to mandate such a study.

VIIIb. Recommendation

Approvable, based on the chemistry deficiencies as listed.

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/s/

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CLINICAL REVIEW

Application Type NDA
Submission Number 22-028
Submission Code N 000

Letter Date Feb. 3, 2006
Stamp Date Feb. 6, 2006
PDUFA Goal Date Dec. 6, 2006

Reviewer Name William Lubas, M.D., Ph.D.
Review Completion Date Nov. 27, 2006

Established Name Cosyntropin Injection
(Proposed) Trade Name none
Therapeutic Class Adrenal/ACTH
Applicant Sandoz Canada Inc.

Priority Designation S

Formulation Injection
Dosing Regimen 0.25 mg/mL, single dose
Indication Diagnostic agent in the screening
of patients presumed to have
adrenocortical insufficiency
Intended Population Patients with presumed
adrenocortical insufficiency

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

There are no clinical deficiencies in this 505(b)(2) application for Cosyntropin Injection, however, the chemistry deficiencies and the results from the DSI inspection still need to be addressed before this application can be approved. Therefore, this application should receive an "approvable" recommendation.

1.2 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

1.2.1 Risk Management Activity

No risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

There are no phase 4 commitments.

1.2.3 Other Phase 4 Requests

It is suggested that the sponsor monitor closely for adverse events that may be associated with an increased immune response with the lower pH formulation.

It is suggested that the sponsor get additional pharmacodynamic and safety data in pediatric patients including children 2 and under.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cosyntropin Injection contains an open chain synthetic polypeptide with the first 24 N-terminal amino acids of natural ACTH (39 amino acids). The sponsor is seeking an indication for use of Cosyntropin as a diagnostic agent in adrenocortical insufficiency. Cosyntropin is formulated as a stable aqueous solution titrated to acidic pH (— with glacial acetic acid for intravenous injection. The reference product, Cortrosyn, currently approved for diagnostic testing in adrenocortical insufficiency contains the same synthetic polypeptide, as a lyophilized powder. Cortrosyn can be given as an IM or IV injection but must be reconstituted with normal saline prior to use. No PK or bridging toxicology studies were required for this new formulation as the

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sponsor was able to show a similar impurity profile to the reference product. This submission includes a single, randomized, blinded, two-way, cross-over pharmacodynamic (PD) study measuring plasma cortisol levels following single intravenous dosing with Cortrosyn and Cosyntropin.

1.3.2 Efficacy

Cosyntropin and Cortrosyn were demonstrated to be bioequivalent with respect to their pharmacodynamic effect on plasma cortisol levels (AUC and Cmax) and so are equally effective for use as diagnostic agents in the screening of patients presumed to have adrenocortical insufficiency.

1.3.3 Safety

There were no adverse events that could directly be related to the study drug in this submission. While there were slightly more adverse reactions in the Cosyntropin group, this difference was not statistically significant and there was no clear difference in the pattern of adverse events seen with Cosyntropin compared to the reference standard Cortrosyn.

Since Cosyntropin has a lower pH, compared to Cortrosyn, which is reconstituted in normal saline, there is a theoretical concern of greater morbidity following extravasation from the IV site. There were no clear cases of extravasation reported in the one clinical trial presented in this submission to support such a concern, but there were only 24 subjects in this trial. There were 3 adverse events associated with the IV site in patients following administration of Cosyntropin compared to only 1 case following administration of the reference product, but none of these adverse events were considered serious.

While neutralizing antibodies are a theoretical concern there is not enough evidence at this time to suggest that they are likely to be more of a problem with Cosyntropin compared to the reference product. Therefore, in this medical officer's opinion, this new formulation is approvable and the drug can be monitored during post marketing surveillance for any increased frequency of immune mediated adverse events.

1.3.4 Dosing Regimen and Administration

The product is to be administered as a single 1ml intravenous dose of the 0.25mg/mL solution i.e. 0.250 mg. In pediatric patients 2 and under a dose of 0.5mL or 0.125 mg may suffice.

1.3.5 Drug-Drug Interactions

No information about drug-drug interactions was included in this submission.

1.3.6 Special Populations

No information about use in special populations was included in this submission.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Sandoz Canada Inc. is seeking an indication for use of Cosyntropin as a diagnostic agent in adrenocortical insufficiency. A normal response in most patients is typically described as a doubling of the basal plasma cortisol level during the initial 60 minutes after dosing, provided that the basal level is not outside the normal range. However, since plasma cortisol levels in patients with normal adrenal function may not always respond to the expected degree the following criteria have been established to denote a normal response.

1. the control plasma cortisol level should exceed 5mcgs/100mL
2. the 30-minute level should show an increment of at least 7mcgs/100mL above the basal level
3. the 30-minute level should exceed 18mcgs/100mL

This application is being filed under 505(b)(2) of the FD&C Act referencing Cortrosyn (cosyntropin) for injection approved under NDA 16-750. The application includes

1. a product impurity comparison to the reference product Cortrosyn
2. a single pharmacodynamic bioequivalence study comparing the plasma cortisol concentration response following intravenous injection of 0.25mg of Cosyntropin and 0.25mg of the reference product Cortrosyn
3. a literature search containing more supportive safety and efficacy information for cosyntropin

2.2 Currently Available Treatment for Indications

Cortrosyn for injection is a sterile lyophilized powder, currently available for use as a diagnostic agent in adrenocortical insufficiency, which must be reconstituted with 0.9% sodium chloride prior to intravenous or intramuscular injection. The Sandoz product, Cosyntropin, differs from the currently marketed product because it is already in solution and does not require reconstitution and because it can only be given via the intravenous (IV) route. Because of these differences the label for Cosyntropin will not be identical to the currently approved product, Cortrosyn, and Cosyntropin cannot be submitted as an abbreviated NDA under 505(j).

2.3 Availability of Proposed Active Ingredient in the United States

Cortrosyn is manufactured by Amphastar Pharmaceutical Inc., Rancho Cucamonga, CA. and is available in the United States.

2.4 Important Issues With Pharmacologically Related Products

None.

2.5 Presubmission Regulatory Activity

In a preNDA meeting with the sponsor, on Sept. 22, 2004, the agency agreed to accept this application under section 505(b)(2).

The agency agreed that if the impurity profile was not significantly different from the reference product that no bridging toxicology studies would be necessary.

The agency agreed that no PK study would be required for an IV only formulation, but that instead a randomized, blinded, two-way cross-over pharmacodynamic (PD) study should be conducted using plasma cortisol levels as the PD endpoint.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Cosyntropin, is an open chain synthetic polypeptide containing the first N-terminal 24 out of the 39 amino acids of natural ACTH. It is formulated as a stable aqueous solution titrated to acidic pH () with glacial acetic acid. b(4)

The chemistry submission contained the following two major deficiencies:

- 1) No bioassay data was submitted for either the drug substance or drug product to permit assessment of lot-to-lot bioactivity and comparison of product performance after manufacturing changes.
- 2) Insufficient data on drug impurities and degradation products was provided to permit adequate stability testing and estimation of expiration dates for the product.

Chemistry has issued an "approvable" recommendation pending the sponsor's response to these deficiencies. For a detailed review of the chemistry submission see Dr. Martin Haber's review.

3.2 Animal Pharmacology/Toxicology

No new information was submitted. The drug product impurity profile was similar between the new formulation and the already marketed product, and as such the sponsor is referencing the nonclinical information from Cortrosyn, NDA 16-750, as agreed to at the preNDA meeting.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data was submitted primarily as a paper submission, with draft labeling, and datasets for clinpharm study 50525 also submitted electronically (\Cdsesub1\N22028\N_000\2006-02-03\Crt\datasets).

4.2 Tables of Clinical Studies

The only new clinical study submitted in this submission was PD study 50525.

Study	Objectives of study	Population	Design
50525	PD study comparing intravenous Cosyntropin (0.25mg) and Cortrosyn (0.25mg)	24 adults (13 male) 21-55 yrs/ healthy	Randomized, single-dose, open-label, 2-way cross-over study

Twelve literature references supporting the efficacy of cosyntropin (1 to 250mcg/dose) were also submitted:

Study population	Number/Age/Condition	Reference/Module 5
Patients and Controls	9/adult/moderate to severe nonendocrine illnesses 7 primary, 2 secondary) 9 control	Speckert 1971 Vol. 7, 5.4.31
Patients	200/na/patients with hypothalamic-pituitary disorders	Lindholm 1987 Vol. 7, 5.4.23
Healthy volunteers	10(5 males)/17-42yrs/ healthy	Hawkins 1989 Vol. 7, 5.4.16
Three groups: 2 patients; 1 volunteer	G 1: 7(3 male)/37.2 yrs./healthy G 2: 10(8 male)/49.4 yrs./pituitary disease HPA Axis G3: 9(5 male)/47.8 yrs./pituitary disease	Tordjman 1998 Vol. 7, 5.4.33
Healthy volunteers and patients	46 (23 male)/33.2 yrs./healthy 37(14 male)/47 yrs./hypothalamic-pituitary-adrenal axis disorders	González-González 1998 Vol. 7, 5.4.12
Patients and controls	57 (31 male)/19-73 yrs./ hypothalamic disorders 18 healthy (7 male) 19-46 yrs.	Ambrosi 1998 Vol. 7, 5.4.1
Patient & Families	13 families/na/adrenal hyperplasia	Kreutzmann 1989 Vol. 7, 5.4.21
Patients and healthy controls	24(12 male)/16-60yrs/secondary hypercortisolism 8(5 male)/na/healthy	Talwar 1998 Vol. 7, 5.4.32
Healthy Volunteers	41 female/29.1yrs/ healthy	Azziz 1990 Vol. 7, 5.4.2
Patients and healthy controls	21 patients/ 12-63 yrs./renal amyloidosis 16 controls/21-52 yrs./healthy	Gündüz 2001 Vol. 7, 5.4.15
Patients and healthy controls	44(19 male)/26-78yrs/mild forms -pituitary disease 35(18 male)/23-90yrs/healthy (20) in-patients(15)	Mayerknecht 2005 Vol. 7, 5.4.25

4.3 Review Strategy

The medical and clinical pharmacology reviewers performed independent reviews, but collaborated with each other during the review process. There was no need for a statistical review of this submission.

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4.4 Data Quality and Integrity

A clinical audit of the single study site _____ was conducted. The results of this inspection were still pending at the time this review was completed.

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4.5 Compliance with Good Clinical Practices

Study 50525 was conducted in accordance with acceptable ethical standards and in compliance with Good Clinical Practice Rules.

4.6 Financial Disclosures

The sponsor provided form FDA 3454 and signed financial disclosure statements certifying that no financial arrangements or interests were held by all nine of the clinical investigators involved in Study 50525 performed at _____

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new data was included in this submission.

5.2 Pharmacodynamics

The new pharmacodynamic data from Study 50525 is presented in Section 6. Integrated Review of Efficacy.

5.3 Exposure-Response Relationships

No new data was included in this submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

For use as a diagnostic agent in the screening of patients presumed to have adrenocortical deficiency.

6.1.1 Methods

The clinical data reviewed in this submission is listed in section 4.1. There was only one new clinical study in this submission (i.e. Study 50525), which is described in sections 6.1.3 and 6.1.4.

6.1.2 General Discussion of Endpoints

The endpoints in Study 50525 were the relative ratios in AUC and Cmax of plasma cortisol after single IV dosing with Cortrosyn and Cosyntropin. AUC and Cmax are standard endpoints typically used to compare bioequivalence between drugs. In this study it was appropriate to look at plasma levels of the PD parameter, cortisol, instead of PK drug levels of Cortrosyn and Cosyntropin since it is plasma cortisol levels which are used for diagnosing adrenocortical deficiency.

6.1.3 Study Design

STUDY DESIGN

This is a single-center, randomized, single-dose, open-label, two-period, crossover, bioequivalence study comparing the plasma cortisol concentration response of Cosyntropin to Cortrosyn under fasting conditions.

INCLUSION CRITERIA (including but not limited to)-

- male or female nonsmokers 18 years of age or older
- BMI 19 to 30 kg/m²

EXCLUSION CRITERIA (including but not limited to)-

- history of illness or surgery within 4 weeks prior to dosing
- history of clinical significant gastrointestinal, neurological, endocrine, cardiovascular, pulmonary, hepatic, immunologic, psychiatric, or metabolic disease
- allergic reactions to cosyntropin or related drugs
- abnormal physical examination, vital signs, ECG or lab screening tests, including an abnormal cortisol level at screening
- hepatitis C antibody, hepatitis B surface antigen or HIV positive
- history of alcohol or drug abuse within 1 year of the study
- use of tobacco products in the 3 months preceding the trial or a positive cotinine test at screening
- pregnancy, breast-feeding, or female subject of child bearing potential having unprotected sex within 14 days of the study
- use of prescription drugs within 14 days of the study or use of drugs that induce or inhibit hepatic drug metabolism within 30 days of the study
- use of over the counter drugs within 7 days of the study

TREATMENT

Subjects were admitted to the _____ on the evening before study dosing. A randomized single dose of Cosyntropin or Cortrosyn was administered after an overnight fast of at least 10 hours in Period 1. The study medication was administered as a single IV bolus over 2 minutes. Subjects continued to fast, except for water, for a period of at least 4 hours after drug administration. Blood samples were taken at -1, -0.5, -0.25, 0.167, 0.33, 0.5, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 hours post dose. Subjects were discharged 8 hours post dosing and readmitted 5 days later to receive the alternative study medication in Period 2. Blood samples were taken at -1, -0.5, -0.25, 0.167, 0.33, 0.5, 0.667, 0.75, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 hours post dose. Subjects were discharged 8 hours post dosing. A post study evaluation including hematology, and biochemistry lab tests, vital signs, urine pregnancy test, urinalysis, and adverse event monitoring, was performed within 14 days of study completion.

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6.1.4 Efficacy Findings

PHARMACODYNAMIC/EFFICACY RESULTS

Plasma cortisol levels were measured from 0 to 6 hours post dosing with Cosyntropin or Cortrosyn. AUC, C_{max} and T_{max} values corrected for baseline cortisol are reported in Table 1 and are similar for both Cosyntropin and Cortrosyn.

Table 1- Baseline Corrected Plasma Cortisol Levels.

Pharmacodynamic Parameters

Parameters	Test (Cosyntropin (A))			Reference (Cortrosyn (B))		
	Mean	± SD	CV (%)	Mean	± SD	CV (%)
AUC _{0-t} (ng·h/mL)	470.39	± 166.76	35.45	481.19	± 222.63	46.27
AUC _{0-inf} (ng·h/mL)	480.69	± 166.35	34.61	504.30	± 214.33	42.50
AUC _{0-inf} (%)	97.66	± 2.28	2.34	93.25	± 10.24	10.98
C _{max} (ng/mL)	153.02	± 38.90	25.42	152.50	± 50.88	33.36
T _{max} (h)	2.31	± 0.55	23.63	2.27	± 0.39	17.28
T _{max} [*] (h)	2.25	± 0.51	-	2.50	± 0.50	-
K _{el} (h ⁻¹)	1.7561	± 0.8628	49.13	1.1732	± 0.3860	32.90
T _{1/2el} (h)	0.46	± 0.16	34.25	0.69	± 0.40	57.93

(N=22) * Medians and interquartile ranges are presented.

Data taken from sponsor's Table 2.7.1-1

Plasma levels of Cosyntropin or Cortrosyn were not measured in this study so a formal pharmacokinetic bioequivalence determination is not possible. However, the study was designed to look at bioequivalence with respect to the pharmacodynamic parameter cortisol, and used a similar prespecified criteria for bioequivalence of 80 to 125% for the 90% geometric confidence intervals of the ratio of least-squares means from the ANOVA of the ln-transformed AUC_{0-t}, AUC_{0-∞} and C_{max}. The results for all 22 subjects are reported in the top part of Table 2, and

show that while $AUC_{0-\infty}$ and C_{max} were within the 80 to 125% range, the upper limit of the AUC_{0-t} was slightly outside that range at 126.47%.

**Table 2- Baseline Corrected Plasma Cortisol Levels. (N=22)
 Cosyntropin (A) vs Cortrosyn (B)**

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio ¹	106.96%	100.99%	104.15%
90 % Geometric C.I. ²	90.45 % to 126.47 %	87.61 % to 116.41 %	92.54 % to 117.23 %
Intra-Subject CV	32.94 %	27.73 %	22.94 %

N = 21, Analysis Excluding Subject No. 05

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio ¹	104.54%	98.91%	103.05%
90 % Geometric C.I. ²	87.89 % to 124.34 %	85.43 % to 114.52 %	91.03 % to 116.65 %
Intra-Subject CV	33.02 %	27.69 %	23.31 %

¹ Calculated using least-squares means according to the formula: $e^{(C_{Cosyntropin(A)} - C_{Cortrosyn(B)})} \times 100$

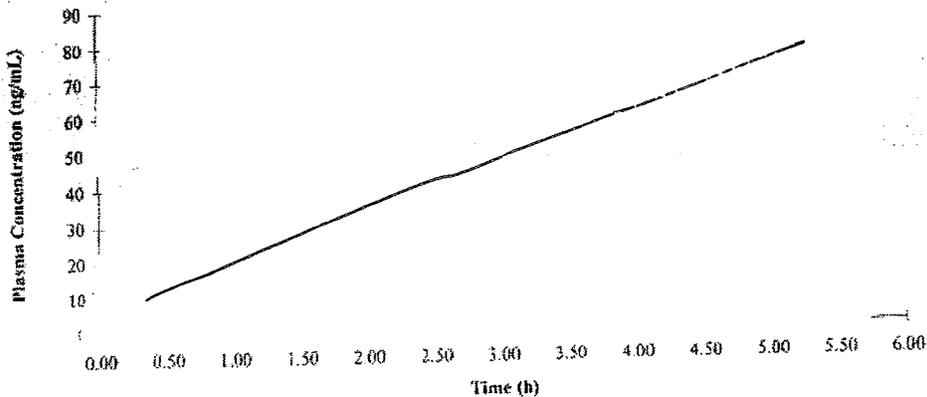
² 90% Geometric Confidence Interval using ln-transformed data

Data taken from sponsor's Tables 2.7.1-2 and 2.7.1-3.

This can largely be attributed to an aberrant result from one subject, No. 05, whose 30 minute corrected value for cortisol was negative following administration with Cortrosyn.

Figure 1

Time Profile for Subject No. 05



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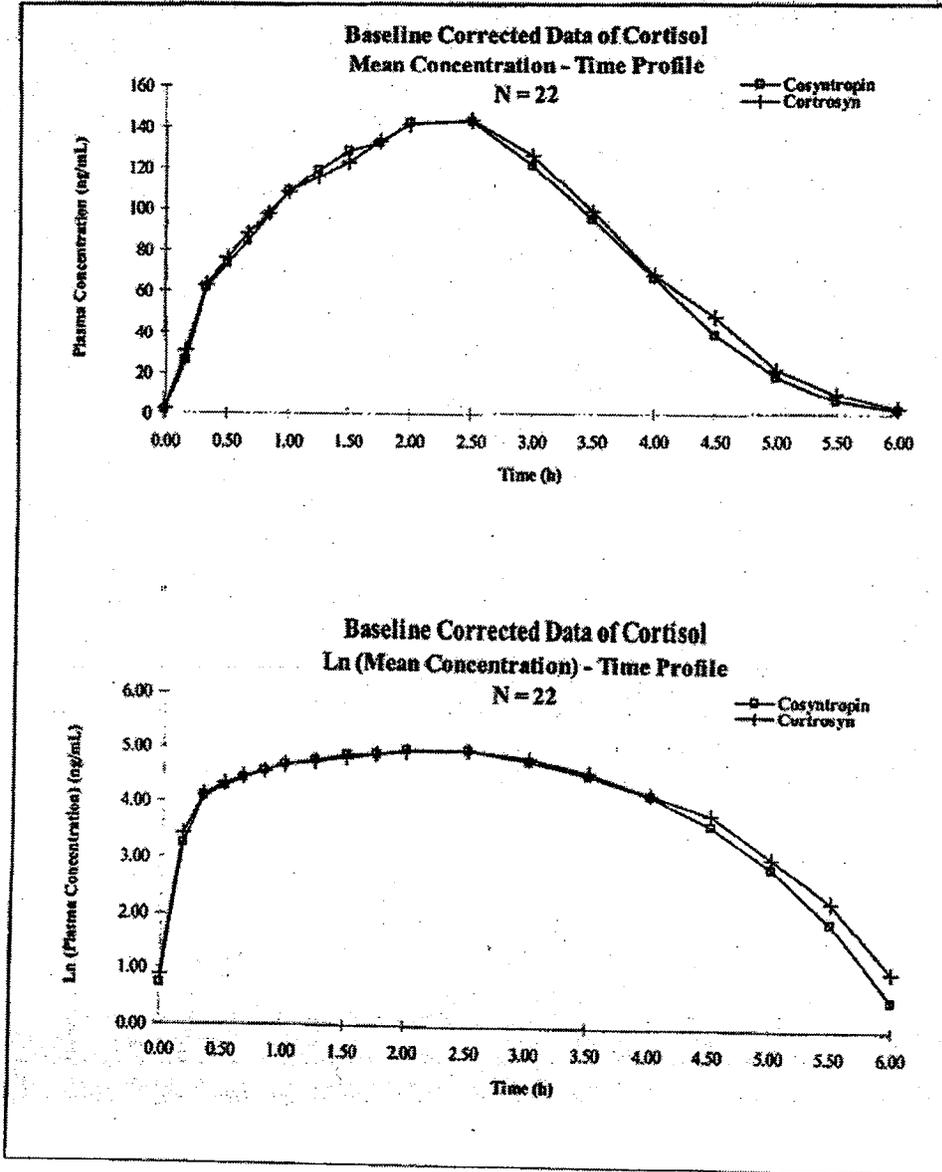
Data taken from sponsor's Fig. 04a section 5.3.1.2.1 pg 111.

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If the data from this one patient is excluded, as is shown in the bottom part of Table 2, all three parameters AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} are within the 80 to 125% range used to demonstrate bioequivalence.

Plots of baseline corrected plasma cortisol and natural log of baseline corrected plasma cortisol over time are shown in Figure 2. Both Cosyntropin and Cortrosyn produce a similar cortisol response over the initial 60 minutes after dosing, the time period used to screen subjects for adrenocortical insufficiency, demonstrating that both drugs are equally effective for screening of patients with presumed adrenocortical axis insufficiency.

Figure 2-
Baseline Corrected Plasma Cortisol or Natural Log of Plasma Cortisol Over Time



(Sponsor's Figures 23a and 23b Section 5.3.1.2.1 pg 130)

6.1.5 Clinical Microbiology

No new data was included in this submission.

6.1.6 Efficacy Conclusions

Cortrosyn and Cosyntropin are bioequivalent with respect to their pharmacodynamic effect on plasma cortisol levels and so are equally effective for use as diagnostic agents in the screening of patients presumed to have adrenocortical insufficiency.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the PD study submitted in this application.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in the PD study submitted in this application.

7.1.3 Dropouts and Other Significant Adverse Events

Out of the 24 healthy patients who were dosed 22 completed the PD study.

With the lower pH in the new formulation there is a theoretical concern of greater morbidity following extravasation from the IV site. There were no clear cases of extravasation reported in the one clinical trial presented in this submission to support such a concern. There were 3 AEs associated with the IV site in patients following administration of Cosyntropin compared to only 1 case following administration of the reference product.

Cosyntropin AEs

1. Mild redness at the catheter site beginning at 34 minutes after dose administration and ending at 7 hours post dose. Considered unrelated to the study drug by treating physician.
2. Moderate pain in the right arm beginning 3 hrs and 52 min after dose administration which was unresolved at the time of discharge but which required no further follow up care. Considered remotely related to the study drug by treating physician.
3. Mild bruise at venipuncture site beginning about 4 ½ days after dose administration but which required no further follow up care. Considered unrelated to the study drug by treating physician.

Cortrosyn AEs

1. Mild pain in the right arm beginning 3 hrs and 46 min after dose administration and ending at 5 hrs and 16min post dose. Considered unrelated to the study drug by treating physician.

7.1.4 Other Search Strategies

None.

7.1.5 Common Adverse Events

While there appear to be slightly more AEs in the Cosyntropin group (see Table 3), they are all mild to moderate in severity and were only remotely related to administration of the study drug.

Table 3		
Adverse Events Reported in Study 50525		
Adverse Event	Cosyntropin	Cortrosyn
Gastrointestinal		
Abdominal pain	1	0
Heartburn	2	1
Nausea	1	0
Cardiovascular		
Decrease in BP	1	0
Decrease in HR	0	1
Increase in HR	0	1
Musculoskeletal		
Pain/redness at catheter site	3	1
Pain at another site	0	2
General		
Burning sensation in throat	1	0
Drowsiness	1	0
Hot flashes	2	0
Nervous System		
Dizziness	1	1
Labs Abnormal		
Hematocrit	0	1
Hemoglobin	0	1
Total	13	9
Data taken from Module 5 Vol. 1 section 14.5.1. One patient could have multiple events. Post dose data.		

These data do not represent a serious safety concern with the new formulation.

Medical Officer's comments-Even though Cosyntropin will be labeled for IV use only, there is always the possibility that it may be mistaken for Cortrosyn and given inadvertently via an IM route. With a more acidic pH the Cosyntropin formulation is more likely to be associated with adverse tissue reactions. The sponsor did not observe any severe localized reactions during the clinical trials, and they recommended "A cool compress" in the case of injection site reactions.

DMETS was asked to consult on this issue and recommended a boxed warning to the container label stating:

*Note: for Intravenous Use Only
Not to be administered by the intramuscular route*

and additional changes to the DOSAGE AND ADMINISTRATION section of the label (see section 9.5 Comments to Applicant).

7.1.6 Less Common Adverse Events

All adverse events were listed in Table. 3, see section 7.1.5.

7.1.7 Laboratory Findings

One patient was noted to have abnormal laboratory values at the end of the study (hemoglobin 10.4mg/dl and hematocrit 31.2%), probably related to excessive phlebotomy, and was sent to a family physician for follow up care. All other laboratory tests were within normal limits.

7.1.10 Immunogenicity

It is possible that the change in pH in the new formulation may affect antibody formation. However, in the majority of cases the presence of an antibody response has no clinical consequence, unless the antibodies are neutralizing or result in an anaphylactic or allergic reaction.

Since the sponsor is seeking an indication for single dose usage, antibody production is less of a concern.

Since the new product will only be administered intravenously, it is less likely to stimulate antibody formation than the reference product, which can also be administered by intramuscular administration.

Since the new product is already presolubilized and presterilized it is likely to have fewer aggregates than the reference product and therefore less likely to stimulate antibody formation associated with the presence of aggregates.

Medical Officer's comments- While neutralizing antibodies are a theoretical concern there is not enough evidence at this time to suggest that this is likely to be more of a problem with Cosyntropin compared to the reference product. Therefore, it is this medical officer's opinion, that this should not prevent approval of this drug application. It is recommended instead that the sponsor monitor for adverse events that may suggest an increased immune response during post marketing surveillance.

7.2 Adequacy of Patient Exposure and Safety Assessments

There were 13 males and 11 females that received at least one dose of the study medication; 22 of those enrolled completed the study. The age range of the healthy volunteers was between 21 and 55 with a mean of 36yrs (SD 11yrs). Their weight ranged between 52.0 and 88.6kg with a mean of 70.5kg (SD 11.4kg). BMI measurements were between 20.1 and 28.4 with a mean of 24.0 (SD 2.1). The patient population was adequate to assess efficacy and safety in adults. There was no need for a 4-month safety update for this single dose indication.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no clearly identified drug-related adverse events in Study 50525. The few cases of mild intravenous site local reactions that were seen could be attributed to the procedure itself.

The data was limited as no pediatric patients were included in Study 50525.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Cosyntropin is to be administered as a single 1mL intravenous dose of a 0.25mg/mL solution (i.e. 0.250 mg).

8.2 Drug-Drug Interactions

No drug-drug interaction studies were submitted.

8.3 Special Populations

This study had too few patients to compare differences in study subgroups.

8.4 Pediatrics

ACTH stimulation tests are performed in the pediatric population. Three references included by the sponsor in this submission included pediatric populations which were being investigated for possible adrenocortical suppression:

Pediatric Population	Dosing
premature (24 to 33wk) very low birth weight newborns (<1500g, n=34) ¹	3.5mcg/kg cosyntropin IV or IM
infants with congenital diaphragmatic hernias (n=6) ²	0.125mg cosyntropin IV
children on high dose inhaled steroids for asthma (n=50) ³	0.125mg tetracosactride IM

No pediatric data was submitted by the sponsor. The innovator product label mentions that half the usual dose (i.e. 0.125mg) will suffice for children 2 years of age and under, but gives no data to support this recommendation. This lower dose was used in two of the previous references^{2,3}. The 1997 JB Handbook 4th edition recommends a dose in children based on body surface area i.e. 250mcg per 1.73m², but no data is included to support how this dose was determined. The 2000-20001 Pediatric Dosage Handbook recommends doses of 0.015mg/kg/dose in neonates (higher than the dose in reference 1), 0.125mg in children under 2 years of age (similar to the dose in references 2 and 3) and a dose of 0.250mg in children over 2 years of age (similar to the dose in the innovator product label).

Medical Officer's comments-Since this product is likely to be used in the pediatric population it seems reasonable to request pharmacodynamic data in this patient population. Recent publications have suggested that low dose ACTH testing with 1 mcg may actually be more sensitive in identifying subjects with adrenal insufficiency, so that even the recommendation of half the dose in younger children (i.e. 125mcg) may be unnecessarily high for maximal efficacy. However, this may be a moot issue as there is no evidence to suggest greater safety risk at single doses up to 250mcg, and dosing needs to take both efficacy and safety into account. Since there are unlikely to be significant safety issues with this single dose product at the currently recommended doses, this medical reviewer recommends approval of the current innovator product dosing information and suggests that the sponsor get additional pharmacokinetic and safety data in pediatric patients as part of an elective post marketing request.

1 Watterberg, K.L. and Scott, S.M. 1995 Pediatrics 95: 120-125

2 Pittinger, T.P. and Sawin, R.S. 2000 J of Ped Surg 35: 223-226

3 Sim, D. et al. 2003 Eur Respir J 21:633-636

8.5 Advisory Committee Meeting

There was no advisory committee meeting.

8.6 Literature Review

The ACTH stimulation test is a safer and more convenient method to measure hypothalamic-pituitary-adrenocortical function than the insulin-induced hypoglycemia or metyrapone tests. The synthetic polypeptide, cosyntropin, containing only the first 24 amino acids of ACTH, has been shown to be as effective but less antigenic than ACTH extracts and is the current drug of choice for use in ACTH stimulation testing. However, occasional allergic reactions have been reported with this synthetic polypeptide. In a group of 292 patients who received repeat doses of cosyntropin, off-label for the treatment of multiple sclerosis, two female patients developed anaphylaxis, one after the 6th injection and one after the 22nd injection⁴. Anaphylaxis is unlikely to be a problem with the single dosing routinely used in adrenocortical insufficiency testing.

8.7 Postmarketing Risk Management Plan

There is no need for a post marketing risk assessment plan.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

- Cosyntropin Injection and Cortrosyn are bioequivalent as diagnostic agents in the screening of patients presumed to have adrenocortical insufficiency.
- The chemistry deficiencies will need to be addressed before this application can be approved.
- The results of the DSI inspection still need to be reviewed before this application can be approved.

9.2 Recommendation on Regulatory Action

There are no clinical deficiencies in this 505(b)(2) application for Cosyntropin Injection, however, the chemistry deficiencies and the results from the DSI inspection still need to be

⁴ Kanic, M and Sepcic J. 1992 Lijec Vjesn May-Aug; 114(5-8): 134-6

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addressed before this application can be approved. Therefore, this application should receive an "approvable" recommendation.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

9.3.1 Risk Management Activity

No risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

It is suggested that the sponsor monitor closely for adverse events that may be associated with an increased immune response with the lower pH formulation and from inappropriate intramuscular injection of this intravenous formulation.

It is suggested that the sponsor get additional pharmacodynamic and safety data in pediatric patients including children 2 years of age and under.

9.4 Labeling Review

The sponsor has a similar label to that of the reference product, Cortrosyn® with the following exceptions:

- The proprietary name Cortrosyn® has been replaced with Cosyntropin Injection
- Under the Description section the new formulation of Cosyntropin is described (i.e. Cosyntropin is a 1ml sterile solution containing 0.25mg of cosyntropin, 0.82 mg of sodium acetate trihydrate, 6.4 mg of sodium chloride, 10 mg of mannitol, 1mg of glacial acetic acid, and water for injection) and mention of use via intramuscular injection has been removed.
- Under the Dosage and Administration section use via intramuscular injection and references for the need to reconstitute prior to use have been deleted.
- Under the How Supplied section storage conditions have been revised to require storage under refrigeration and protection from light and freezing.

Specific labeling recommendations to lower the possibility that this product may be accidentally interchanged for Cortrosyn and given IM instead of IV are included in Section 9.5.

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9.5 Comments to Applicant

1. Include a boxed warning on the container label that states:
Note: For Intravenous Use Only
Not to be administered by the intramuscular route
2. The Cortrosyn labels use similar colors with their trade dress (blue on white background). We strongly recommend that you revise your color scheme so your labels and labeling appear entirely different from Organon's Cortrosyn. This visual similarity in conjunction with the fact that your product does not have a proprietary name increases the risk of product interchangeability and selection errors.
3. The presentation of the sponsor's name and log is more prominent than the established name. Revise the presentation so that the proprietary and established names are the most prominent information on the primary display panel.
4. Include a net quantity statement on the principal display panel (e.g. 1 mL) and ensure that it is not in close proximity to the strength. We refer you to 21 CFR 201.51 for further guidance.
5. In the carton labeling decrease the size of the "FOR DIAGNOSTIC USE ONLY" statement, and revise the "10 Single-Dose Vials" statement to read "10 - 1mL single dose vials".
6. Under ADVERSE REACTIONS " _____ should be changed to " _____ or the entire sentence can be deleted.
7. Under DOSAGE AND ADMINISTRATION in the first paragraph after describing intravenous injection and infusions a statement describing that this product should not be given intramuscularly should be inserted.
8. Under DOSAGE AND ADMINISTRATION the statement "The drug product should be visually inspected for particular matter ..." should be placed before the sentence "Inject 1ml of cosyntropin injection."
9. Under DOSAGE AND ADMINISTRATION clearly identify the "glucose" and "saline" solutions, including their strengths which can be mixed with cosyntropin (e.g. 5% Dextrose, _____, 0.9% Sodium Chloride etc.) prior to injection and remove the statement " _____"
10. Under DOSAGE AND ADMINISTRATION "Cosyntropin injection should not be retained." should be replaced with "Unused cosyntropin injection should be discarded."
11. Under DOSAGE AND ADMINISTRATION " _____"

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10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable

10.2 Line-by-Line Labeling Review

Specific labeling recommendations were included in Section 9.5 Comments to Applicant.

REFERENCES

- 1 Watterberg, K.L. and Scott, S.M. 1995 Pediatrics 95: 120-125
- 2 Pittinger, T.P. and Sawin, R.S. 2000 J of Ped Surg 35: 223-226
- 3 Sim, D. et al. 2003 Eur Respir J 21:633-636
- 4 Kanic, M and Sepcic J. 1992 Lijec Vjesn May-Aug; 114(5-8): 134-6

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/s/

William Lubas
11/27/2006 03:05:20 PM
MEDICAL OFFICER

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