CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-028

PHARMACOLOGY REVIEW(S)

Signed into DFS on 1/16/2008.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-028
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	8/21/2007
PRODUCT:	Cosyntropin
INTENDED CLINICAL POPULATION:	Diagnostic agent in the screening of patients with adenocortical insufficiency.
SPONSOR:	Sandoz Inc., Bloomfield, CO.
DOCUMENTS REVIEWED:	One volume, submitted on 8/20//07.
REVIEW DIVISION:	Division of Metabolism and Endocrinology Products.
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis Bruno
DIVISION DIRECTOR:	Mary parks
PROJECT MANAGER:	Jena Weber

Date of review submission to Division File System (DFS): 1/16/2008

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Executive Summary

1. Recommendations

A. **Recommendation on approvability**

Pharmacology recommends conditional approval of this drug for proposed single use.

B. **Recommendation for Nonclinical Studies**:

The preclinical studies are not required for this drug product, since the reference listed drug (RLD) cortrosyn has been marketed since 1970 under NDA 16-750 in a lyophilized powder form. No animal studies were required for previously approved cortrosyn also, because it is a synthetic form of beta 1-24 corticotropin present in the natural product. No carcinogenicity, mutagenicity, impairment of fertility, or repro-tox studies have been conducted with this drug under current or previous NDA. However sponsor did not fully qualify the impurities produced during the manufacturing and storage of their drug substance/product when they initially submitted this application on 2/3/06. In the current application they have provided the supporting data on impurities for chemistry deficiencies and one non-GLP acute preclinical study in mice. The submitted non-GLP acute study is adequate for proposed single use. However, the multiple use marketing would require testing of impurities in a standard toxicity study as per ICH Q3A.

C. **Recommendation on Labeling**: Labeling in general is acceptable, however minor changes have been made. Following labeling changes are recommended as previously suggested in the review of the initial application (signed off in DFS on 10/3/2006) :

1. Pregnancy: Sponsor's proposed labeling on pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with cosyntropin injection, it is also not known whether cosyntropin injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cosyntropin injection should be given to a pregnant woman only if clearly needed.

Reviewer's recommended changes:

Pregnancy Category C. Safety in pregnant women has not been established. There are no adequate and well controlled studies of cosyntropin in pregnant women. Cosyntropin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Nursing Mothers: Sponsor's proposed labeling on nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cosyntropin injection is administered to a nursing woman.

Reviewer's recommended changes:

It is not known whether cosyntropin is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in

nursing infants from cosyntropin, caution should be exercised when cosyntropin injection is administered to a nursing woman.

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies

Tetracosactide (or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). Tetracosactide or α^{1-24} corticotropin is currently a marketed drug in USA since 1970 as a sterile lyophilized powder for iv and im use (as cortrosyn (NDA 16-750). This application is a 505 b(2) which relies on the previous studies on cortrosyn. The current product differs from the marketed cortosyn (NDA 16-750) in that it does not require [redacted]. The current product is an aqueous solution which could be used for iv administration. Sponsor has submitted one acute non-GLP study in mice to qualify the impurity ([redacted]) in the drug substance, which is adequate for proposed single use indication only. However, the multiple use marketing would require testing of impurities in a standard toxicity study as per ICH Q3A. b(4)

B. Pharmacologic activity

Cosyntropin is a synthetic form of beta 1-24 corticotropin present in the natural product. It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. A 0.25 mg dose of cosyntropin stimulates adrenal cortex to produce maximal secretion of 17-OH-corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids. This dose stimulates the adrenal cortex to the same extent as 25 units of natural ACTH.

C. Nonclinical safety issues relevant to clinical use

The impurity in the drug substance has been qualified for acute one time use only. Note that the multiple use marketing of this drug would require testing of impurities in a standard toxicity study as per ICH Q3A. There are no other non-clinical safety issues relevant to the clinical use with the current drug product.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-028
Review Number: 2

Sequence number/date/type of submission: 8/20/2007, one volume. Original application was submitted on 2/3/2006. It is a 505(b)(2) application. The previous NDA (NDA 16-750) of this drug was approved in 1970.

Information to sponsor: Yes ( ) No (X)

Sponsor: Sandoz Inc., Broomfield, Colarado.

b(4)

Manufacturer for drug substance: [redacted]

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolism and Endocrinology Products (DMEP).
Review completion date: 1/15/2008

Drug:

Trade name: Cosyntropin intravenous injection, 0.25 mg/ml.
Generic name (list alphabetically): Alpha (sup 1-24)-corticotropin, cosyntropin
Code name: Tetracosactide, tetracosactin, synacthene.
Chemical Name:

H-L-Seryl-L-Tyrosyl-L-Seryl-L-Methionyl-L-Glutamyl-L-Histidyl-L-Phenylalanil-L-Arginyl-L-Tryptophyl-L-Glycyl-L-Lysyl-L-Prolyl-L-Valyl-L-Glycyl-L-Lysyl-L-Lysyl-L-Arginyl-L-Arginyl-L-Prolyl-L-Valyl-L-Lysyl-L-Valyl-L-Tyrosyl-L-Pro-OH

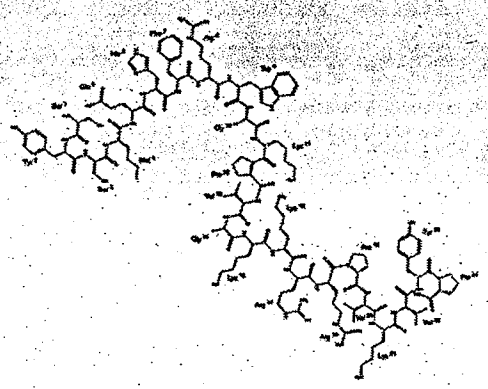
Primary sequence in three letter code:

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro

Primary sequence in one letter code:

S-Y-S-M-E-H-F-R-W-G-K-P-V-G-K-K-R-R-P-V-K-V-Y-P

CAS Registry Number: 16960-16-0
Molecular formula/molecular weight: $C_{1136}H_{210}N_3N_{40}O_{31}$/2933
Structure:



Relevant INDs/NDAs/DMFs: NDA 16-750 (cosyntropin), IND 69,720. DMF number

Drug class: Peptide hormone. Cosyntropin (Tetracosactide) is a synthetic subunit of adrenocorticotropic hormone (ACTH).

Intended clinical population: The drug is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency

Clinical formulation: The formulation containing the active drug and inactive excipients is shown below.

Components	Quantity per unit	Percentage
Tetracosactide	0.25 mg	0.025%
Trihydrated Sodium Acetate	0.82 mg	0.082%
Sodium Chloride	6.4 mg	0.64%
Mannitol	10 mg	1.0%
Glacial Acetic Acid	1 mg	0.1%
Water for Injection	q.s. to 1 mL	
Total		

b(4)

Route of administration: Intravenous (iv).

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed within this submission: This NDA application was originally submitted on 2/3/06. Sponsor was sent an approvable letter on 12/6/06 with a list of chemistry deficiencies. This is because the sponsor had not fully qualified the impurities. Therefore in the current application (8/20/07) sponsor has provided a complete response to the chemistry deficiencies as well as one acute toxicity study in mice to qualify the

impurities and degradation products, which is reviewed. Note that since this is a 505(b)(2) application, studies on the reference listed drug (RLD) were previously reviewed under NDA 16-750 and IND 69,720.

Studies not reviewed within this submission: None

2.6.1 INTRODUCTION AND DRUG HISTORY

Cosyntropin (Tetracosactide or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. Cosyntropin is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

The adrenal insufficiency is a dysfunction which can be present at one or more sites in the hypothalamic pituitary axis (HPA). Administration of ACTH results in a rise in plasma corticosteroid concentration which is an index of the functional reserve of the adrenal cortex. Cortrosyn/Cosyntropin injections exhibit the full corticosteroidogenic activity of natural ACTH. The biological activity of ACTH resides in the N-terminal portion of the molecule and the 1-20 amino acids residue is the minimal sequence retaining full activity. Synthetic ACTH containing 1-24 amino acids has very little immunological activity. The greatest degree of antigenicity resides in the C-terminal portion of natural 39-amino acid molecule and 22-39 amino acid residues exhibit the greatest degree of antigenicity. The synthetic polypeptides containing 1-19 or fewer amino acids have no detectable immunologic activity. In contrast those containing 1-26, 1-24, 1-23 amino acids have very little immunologic, although full biologic activity. The patients presenting with symptoms suggestive of adrenal insufficiency are evaluated to determine whether cortisol production is adequate. Tests that are routinely used for this purpose include the Cortrosyn stimulation test, the insulin tolerance test, the metyrapone test, and serum cortisol levels. The cortrosyn stimulation test is however the standard diagnostic test for adrenal insufficiency. Following diagnosis of adrenal insufficiency the next step is localizing the defect, which is usually accomplished by drawing a plasma ACTH level. In some cases, a prolonged ACTH infusion or corticotrophin-releasing hormone (CRH) test may be used to establish whether the defect is located centrally or at the adrenal glands.

2.6.2 PHARMACOLOGY

A 0.25 mg dose of cosyntropin stimulates the adrenal cortex to produce maximal secretion of 17-OH-corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids. This dose stimulates the adrenal cortex to the same extent as 25 units of natural ACTH. Cosyntropin administered intravenously, is intended for use as a diagnostic agent for adrenocortical insufficiency.

Background for the current submission and Safety evaluation:

The current drug (cosyntropin) is developed based on two existing products, one is Cortrosyn injection (from Amphastar Pharmaceutical, Inc., NDA 16-750) and the other is Synacthene (European product from Novartis). Cortrosyn is currently a marketed drug in USA since 1970 as a sterile lyophilized powder. The marketed cortrosyn vial contains 0.25 mg of the drug (cortrosyn) which needs to be reconstituted with 1 ml of 0.9% sodium chloride and is marketed for intravenous or intramuscular (IM) use. Cortrosyn is used by the current sponsor as the reference listed drug (RLD). The European product Synacthene is not a powder but an injectable solution.

This application was initially submitted on 2/3/06. Pharmacology/toxicology completed the review of this application and recommended for approval (see the review signed off in DFS on 10/3/2006).

However after it was signed off in DFS, the chemistry reviewer had notified the pharmacology/toxicology discipline that the sponsor had misled us and impurities in the drug substance/ product were not fully qualified. The pharmacology/toxicology evaluation of impurities was not possible before, since the sponsor did not provide any data and had indicted that all impurities were below their limit of quantitation.

Sponsor was sent an approvable letter on 12/6/06 with a list of chemistry deficiencies, see part of the letter below (under point 2 in deficiencies, second sentence).

2. In order to determine an acceptable expiration dating period, a complete characterization study report on the impurities and degradation products must be provided, and adequate controls of impurities and degradation products must be part of the drug substance and drug product specifications. Please include the following in the characterization study report on the impurities and degradation products:

- A summary of the actual and potential impurities and degradation products most likely to arise during the manufacture and storage of the drug substance and drug product; a complete summary of laboratory studies conducted to detect impurities and degradation products in the drug substance and drug product, and cross-references to supporting safety data (nonclinical and/or clinical data with the associated lot or batch numbers) as part of your justification of the proposed limits on impurities and degradation products.

The sponsor has now resubmitted this NDA (8/20/07) with a complete response to the listed chemistry deficiencies. They have provided one pre-clinical acute toxicity study in mice to support the impurities and degradation products.

In the above submission (8/20/07), the sponsor identified a new impurity which is [redacted] with a [redacted] The sponsor states that the drug product has impurity of [redacted] in tetracosactide at the level of [redacted]. Sponsor further states that 'as there is no standard for this impurity, this impurity is identified by its relative retention time of around [redacted], the structure of the impurity is shown below:

b(4)

b(4)

This impurity was identified by the drug substance supplier during the stability studies at month-13 under refrigerated conditions (at ——. It is present at levels between — and —. Note that this level of impurity is constant up to time 36 month. Please note this impurity is found at levels of —% (lot TC0401), —% (lot TC0502) and — (lot TC0501) in the drug substance and —% (lot 1200503-F), — (1360504-F) and —, (lot 1350504-F) in the drug product.

b(4)

b(4)

In order to qualify this impurity, the drug substance supplier performed an abnormal toxicity test of a sample containing — impurity.

In this study, five mice (weighing 17-18 g) were injected intravenously (IV) with 10.26 mg/kg of the drug (dissolved in water injected over a period of 15-30 seconds) which contained — mg of impurity (or —, impurity). Mice were observed for 48 hours for mortality and anomalous behavior.

Study dose and human equivalence:

Organism	Sample Dose	—, Impurity Dose
Study Mice (approx. 20 g weight)	10.26 mg/kg (0.21 mg)	
Human Equivalent (approx. 60 kg weight)	10.26 mg/kg (615.6 mg)	

b(4)

With a proposed specification of — impurity level intake would be:

Max. Daily Dose	—, Impurity Dose
1 mg	— ng

The study description is provided below:

2.6.9. ABNORMAL TOXICITY

GENERAL TEST

Inject intravenously into each of 5 healthy mice, weighing 17 g to 22 g, the quantity of the substance to be examined prescribed in the monograph, dissolved in 0.5 ml of *water for injections R* or of a 9 g/l sterile solution of *sodium chloride R*. Inject the solution over a period of 15 s to 30 s, unless otherwise prescribed.

The substance passes the test if none of the mice die within 24 h or within such time as is specified in the individual monograph. If more than one animal dies the preparation fails the test. If one of the animals dies, repeat the test. The substance passes the test if none of the animals in the second group die within the time interval specified.

Results: Sponsor states that no mice died and no signs of toxicity or anomalous behavior was observed, no data were provided. On 10/16/07, we requested the study report for the above abnormal toxicity study, the sponsor provided the report by e-mail on the same day, however no additional data were provided in the results section.

Additionally, sponsor states that the drug product was found to be sensitive to degradation by oxidation, thermal and base treatments but because that these conditions are considered extreme, it is unlikely that these impurities will arise under normal storage conditions.

Overall conclusions and recommendations

Sponsor has conducted an acute toxicity study in mice with the sample containing [redacted] impurity to qualify the impurities, however it is a poorly conducted study and only mortality data were provided. Note that all animals survived the above administered level of impurity. b(4)

The qualification of impurities generally requires in vitro genotoxicity testing as well as 2 to 4 week bridging toxicology study in one species (as per ICH Q3A and ICH Q3B), unless the literature can be provided to adequately support safety.

Cosyntropin is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. The drug will be administered intravenously for one time use only. So acute toxicity study conducted in mice to qualify the new impurity identified can be acceptable. However, it is a poorly conducted study and only mortality was observed in animals. Sponsor did not provide us with the complete data. It is unknown if this was a GLP study and as stated earlier, these and other details were missing.

Since the drug impurity is a [redacted] product, the further genotox testing may not be warranted. b(4)

No bridging toxicity studies were required for this new formulation in the initial application, as sponsor had stated that there was a similar impurity profile as the reference listed drug (RLD cortrosyn, NDA 16-750).

The sponsor is proposing 0.25 mg dose of the current drug for iv injection. Currently the recommended dose of approved cortrosyn is up 0.25 mg iv or im administration in the label. Therefore the doses of the current drug are the same as the approved drug.

This drug is for one time use only as indicted earlier. Cosyntropin is to be administered as a single 1ml intravenous dose of a 0.25mg/mL solution (i.e. 0.250 mg). It will be used for the diagnostic testing. Previous reference listed drug (currently marketed) has no impurity profile (i.e they did not identify any impurities) but has higher levels of impurities than the current drug product, so the current drug appears to be a better product in terms of total impurities present then the approved one. However [redacted] (an impurity here) is not identified in the currently marketed product. In the initial NDA, the drug had total impurities of [redacted] % and now these have been reduced to up to [redacted] b(4)

b(4)

Note that although sponsor states that the impurity was present in the drug substance between [redacted] and [redacted] %, but when six lots of the drug substance and drug product were analyzed, this impurity was found between [redacted] % in the drug substance and [redacted] in the drug product (page 9).

This drug is for single diagnostic use, therefore conditional approval of this application is recommended for single use only (pending labeling changes). The multiple use marketing will require results from impurity testing (qualification) that will involve more than just mortality examinations (i.e. standard toxicity studies). [redacted] is a dietary supplement and likely undergoes [redacted] Toxicity findings as [redacted] require significantly higher exposures than will be achieved in an acute study. There are no data available on the toxicity profile of [redacted] b(4)

Labeling Review: The labeling is in general acceptable. In the previous approved cortrosyn label (not found in the PDR, but copy provided by the sponsor), there were no labeling sections on carcinogenicity, pregnancy or in nursing mothers. However, following minor revisions in the 'pregnancy' and 'nursing mothers' section of the label are recommended as indicated in the initial application signed off in DFS on 10/3/06.

Following is sponsor's suggested label

[redacted] b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-1

Recommendation: The conditional approval of this application is recommended for single use only (pending labeling changes) as the identified impurity (——— ——— , in the drug substance was not qualified in a standard toxicity study. b(4)

The multiple use marketing will require results from impurity testing, i.e qualification of the drug substance impurity (——— , in a standard toxicity study, and not just mortality examinations. Sponsor needs to qualify *any novel excipients/impurities present in the final marketed formulation above the qualification thresholds as per ICH Q3A. These studies would include a 2-4 week toxicity study in one species unless literature can be provided to adequately support safety of these excipients/impurities.* b(4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/lubas/weber
Review code: AP
File name: nda22028/001 (cosyntropin)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
1/16/2008 11:58:00 AM
PHARMACOLOGIST
The conditional approval of this application is recommended for single use only, as the identified impurity in the drug substance was not fully qualified in a standard toxicity study.
The pharmacology recommends conditional approval of this drug for proposed single use only.

Karen Davis-Bruno
1/16/2008 12:06:04 PM
PHARMACOLOGIST

Signed into DFS on 10/3/06.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-028
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	2/6/2006
PRODUCT:	Cosyntropin
INTENDED CLINICAL POPULATION:	Diagnostic agent in the screening of patients with adenocortical insufficiency.
SPONSOR:	Sandoz Inc., Bloomfield, CO.
DOCUMENTS REVIEWED:	Volume 2.1, submitted on 3/13/06.
REVIEW DIVISION:	Division of Metabolism and Endocrinology Products.
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis Bruno
DIVISION DIRECTOR:	Mary parks
PROJECT MANAGER:	Jena Weber

Date of review submission to Division File System (DFS): 10/3/2006

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Executive Summary

1. Recommendations

A. **Recommendation on approvability**

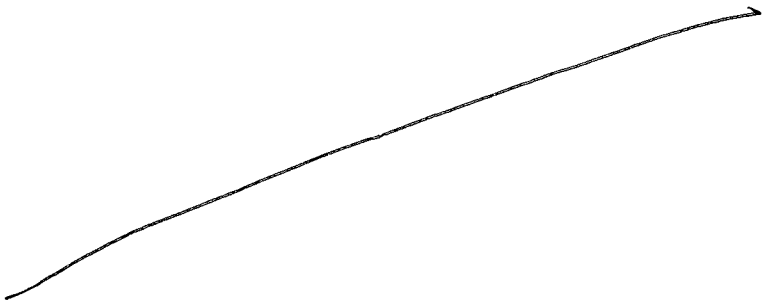
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:

The preclinical studies are not required for this drug product, since the reference listed drug (RLD) cortrosyn has been marketed since 1970 under NDA 16-750 in a lyophilized powder form. No animal studies were required for previously approved cortrosyn also, because it is a synthetic form of beta 1-24 corticotropin present in the natural product. No carcinogenicity, mutagenicity, impairment of fertility, or repro-tox studies have been conducted with this drug under current or previous NDA. Since the RLD (NDA 16-750) was approved in 1970, no further pre-clinical studies are required

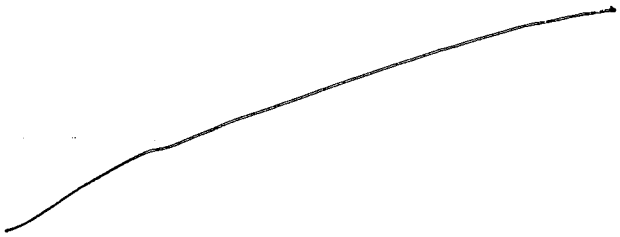
C. **Recommendation on Labeling**: Labeling is in general acceptable, however minor changes have been made. No new pharmacology/toxicity studies have been submitted in the current NDA. Following labeling changes are recommended:

1. Pregnancy: Sponsor's proposed labeling on pregnancy



b(4)

2. Nursing Mothers: Sponsor's proposed labeling on nursing mothers



II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies

Tetracosactide (or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). Tetracosactide or α^{1-24} corticotropin is currently a marketed drug in USA since 1970 as a sterile lyophilized powder for iv and im use (as cortrosyn (NDA 16-750). This application is a 505 b(2) which relies on the previous studies on cortrosyn. The current product differs from the marketed cortosyn (NDA 16-750) in that it does not require [redacted] The current product is an aqueous solution which could be used for iv administration. b(4)

B. Pharmacologic activity

Cosyntropin is a synthetic form of beta 1-24 corticotropin present in the natural product. It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. A 0.25 mg dose of cosyntropin stimulates adrenal cortex to produce maximal secretion of 17-OH-corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids. This dose stimulates the adrenal cortex to the same extent as 25 units of natural ACTH.

C. Nonclinical safety issues relevant to clinical use

There are no new non-clinical safety issues relevant to the clinical use with the current drug product.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 22-028
Review Number: 1

Sequence number/date/type of submission: 2/3/2006 (original application), 3/13/06 (pharmacology/toxicity literature reports, 1 volume). It is a 505(b)(2) application. The previous NDA (NDA 16-750) of this drug was approved in 1970.

Information to sponsor: Yes ( ) No (X)

Sponsor: Sandoz Inc., Broomfield, Colarado.

Manufacturer for drug substance: _____

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolism and Endocrinology Products (DMEP).
Review completion date: 10/3/2006

Drug:

Trade name: Cosyntropin intravenous injection, 0.25 mg/ml.
Generic name (list alphabetically): Alpha (sup 1-24)-corticotropin, cosyntropin
Code name: Tetracosactide, tetracosactin, synacthene.
Chemical Name:

H-L-Seryl-L-Tyrosyl-L-Seryl-L-Methionyl-L-Glutamyl-L-Histidyl-L-Phenylalanil-L-Arginyl-L-Tryptophyl-L-Glycyl-L-Lysyl-L-Prolyl-L-Valyl-L-Glycyl-L-Lysyl-L-Lysyl-L-Arginyl-L-Arginyl-L-Prolyl-L-Valyl-L-Lysyl-L-Valyl-L-Tyrosyl-L-Pro-OH

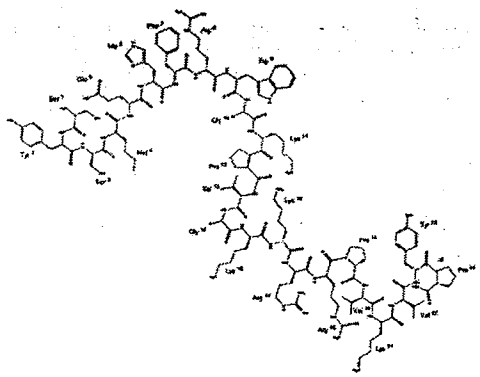
Primary sequence in three letter code:

Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro

Primary sequence in one letter code:

S-Y-S-M-E-H-F-R-W-G-K-P-V-G-K-K-R-R-P-V-K-V-Y-P

CAS Registry Number: 16960-16-0
Molecular formula/molecular weight: $C_{1136}H_{210}N_3N_{40}O_{31}$/2933
Structure:



Relevant INDs/NDAs/DMFs: NDA 16-750 (cosyntropin), IND 69,720. DMF number

Drug class: Peptide hormone. Cosyntropin (Tetracosactide) is a synthetic subunit of adrenocorticotropic hormone (ACTH).

Intended clinical population: The drug is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency

Clinical formulation: The formulation containing the active drug and inactive excipients is shown below.

Components	Quantity per unit	Percentage
Tetracosactide	0.25 mg	0.025%
Trihydrated Sodium Acetate	0.82 mg	0.082%
Sodium Chloride	6.4 mg	0.64%
Mannitol	10 mg	1.0%
Glacial Acetic Acid	1 mg	0.1%
Water for Injection	q.s. to 1 mL	
Total		

b(4)

Route of administration: Intravenous (iv).

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed within this submission: Studies were previously reviewed under NDA 16-750 and IND 69,720. The safety of current drug formulation is reviewed.

Studies not reviewed within this submission: None

2.6.1 INTRODUCTION AND DRUG HISTORY

Cosyntropin (Tetracosactide or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. Cosyntropin is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

The adrenal insufficiency is a dysfunction which can be present at one or more sites in the hypothalamic pituitary axis (HPA). Administration of ACTH results in a rise in plasma corticosteroid concentration which is an index of the functional reserve of the

adrenal cortex. Cortrosyn/Cosyntropin injections exhibit the full corticosteroidogenic activity of natural ACTH. The biological activity of ACTH resides in the N-terminal portion of the molecule and the 1-20 amino acids residue is the minimal sequence retaining full activity. Synthetic ACTH containing 1-24 amino acids has very little immunological activity. The greatest degree of antigenicity resides in the C-terminal portion of natural 39-amino acid molecule and 22-39 amino acid residues exhibit the greatest degree of antigenicity. The synthetic polypeptides containing 1-19 or fewer amino acids have no detectable immunologic activity. In contrast those containing 1-26, 1-24, 1-23 amino acids have very little immunologic, although full biologic activity. The patients presenting with symptoms suggestive of adrenal insufficiency are evaluated to determine whether cortisol production is adequate. Tests that are routinely used for this purpose include the Cortrosyn stimulation test, the insulin tolerance test, the metyrapone test, and serum cortisol levels. The cortrosyn stimulation test is however the standard diagnostic test for adrenal insufficiency. Following diagnosis of adrenal insufficiency the next step is localizing the defect, which is usually accomplished by drawing a plasma ACTH level. In some cases, a prolonged ACTH infusion or corticotrophin-releasing hormone (CRH) test may be used to establish whether the defect is located centrally or at the adrenal glands.

2.6.2 PHARMACOLOGY

A 0.25 mg dose of cosyntropin stimulates the adrenal cortex to produce maximal secretion of 17-OH-corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids. This dose stimulates the adrenal cortex to the same extent as 25 units of natural ACTH. Cosyntropin administered intravenously, is intended for use as a diagnostic agent for adrenocortical insufficiency.

The safety evaluation

The current drug (cosyntropin) is developed based on two existing products, one is Cortrosyn injection (from Amphastar Pharmaceutical, Inc., NDA 16-750) and the other is Synacthene (European product from Novartis). Cortrosyn is currently a marketed drug in USA since 1970 as a sterile lyophilized powder. The marketed cortrosyn vial contains 0.25 mg of the drug (cortrosyn) which needs to be reconstituted with 1 ml of 0.9% sodium chloride and is marketed for intravenous or intramuscular (IM) use. Cortrosyn is used by the current sponsor as the reference listed drug (RLD). The European product Synacthene is not a powder but an injectable solution.

Sponsor wanted to develop a ready to use version of Cortrosyn, therefore they have used both Cortrosyn (powder) and synacthene (an injectable solution) as a basis to develop a stable solution. The current product differs from the marketed cortrosyn (NDA 16-750) in that it does not require ——— , it is in an aqueous solution which could be used for iv administration or infusion (but not for IM administration). b(4)

The sponsor states that they have used validated LC-MS/MS methods to quantify identified and unidentified impurities in the active pharmaceutical ingredient (API) and finished product. Following impurities have been described in cosyntropin API (Table 1)

Table 1. ——— impurities are shown in cosyntropin API. b(4)

impurities potentially be found at levels higher than in the purified API. Identification is proposed for of these impurities; the peak remains an unknown impurity. b(4)

Impurity	Origin

The impurities are Sponsor states that since there is no reference material for impurities (i.e.), these are treated as unidentified impurities. is a known potential degradation product of tetracosactide, this impurity has been limited to no more than (NMT) based on the British Pharmacopia (BP) monograph for tetracosactide injection. The individual impurities are limited to NMT each. b(4)

Table 2. The % Impurities of tetracosactide and corresponding proposed limits are shown below

Impurity	Proposed limit	EP limit	BCN Peptides limit

b(4)

However, the content and purity of the peptide in the API as well as in the finished drug product is similar to the RLD cortrosyn. The results also demonstrate similar impurity profiles with respect to unidentified impurities in both their drug product (cosyntropin) and in the RLD (cortrosyn).

Sponsor states that the impurities/drug product degradants in the RLD drug product were as follows: b(4)

Sponsor further states that in fact the known impurity, is higher in the RLD then in the API of the Sandoz product. Also the byproduct represents only in Cosyntropin vs in the RLD (cortrosyn) as stated below. b(4)

Results have shown that COSYNTROPIN (Tetracosactide Injection) and Cortrosyn® samples both contain a This by-product represents (COSYNTROPIN) and (Cortrosyn®) of the parent Tetracosactide peptide. In addition. Cortrosyn® samples show evidence of a This by-product was not found in COSYNTROPIN samples. b(4)

The Table below also shows that the two marketed drug product formulations have the same active ingredient (Tetracosactide) as the current cosyntropin product formulation, and also contain similar exciepients, with the exception of ingredients added to in cosyntropin. b(4)

Each mL contains:	Cortrosyn® Amphastar	Synacthene® Novartis	COSYNTROPIN Sandoz Canada Inc.
Tetracosactide	0.25 mg	0.25 mg	0.25 mg
Glacial acetic acid	--	1.45 mg [$]	1 mg
Sodium acetate	--	0.51 mg [$] (anhydrous)	0.82 mg (trihydrate)
Sodium chloride	0.9% *	6.08 mg [$]	6.4 mg
Mannitol	10 mg	--	10 mg
[redacted]			
Water for injection	q.s. 1 mL *	q.s. 1 mL	q.s. 1 mL

b(4)

The excipients used in all three formulations conform to USP/NF monograph and are commonly used in other pharmaceutical preparations. The pH of the cosyntropin is adjusted to [redacted], which sponsor states is within the stability range for a solution containing tetracosactide, while the pH of the re-cosnstituted cortrosyn is around [redacted] because this solution is intended to be used immediately.

b(4)

Therefore all the excipients used in the Sandoz formulation have been demonstrated to be compatible with the active pharmaceutical ingredient (API) Tetracosactide.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Cosyntropin (Tetracosactide or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. Its intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

Cortrosyn is currently a marketed drug in USA as a sterile lyophilized powder. The marketed cortrosyn vial contains 0.25 mg of the drug (cortrosyn) which needs to be reconstituted with 1 ml of 0.9% sodium chloride and is marketed for intravenous or intramuscular (IM) use, this product is used by the sponsor as the reference listed drug (RLD). The current product cosyntropin differs from the marketed cortrosyn (NDA 16-750), because it does not require [redacted] Cosyntropin is in an aqueous solution which could be used for iv administration or infusion (but not for intramuscular administration).

b(4)

Safety Evaluation: Supportive information for cosyntropin excipients is provided in the current submission.

The sponsor is proposing 0.25 mg dose of the current drug for iv injection. Currently the recommended dose of approved cortrosyn is up 0.25 mg iv or im administration in the label. Therefore the doses of the current drug are the same as the approved drug.

Labeling Review: The labeling is in general acceptable. In the previous approved cortrosyn label (not found in the PDR, but copy provided by the sponsor), there were no labeling sections on carcinogenicity, pregnancy or in nursing mothers. However,

following minor revisions in the 'pregnancy' and 'nursing mothers' section of the label are recommended:
Following is sponsor's suggested label

1. Sponsor's proposed labeling on **Carcinogenesis, Mutagenesis, Impairment of Fertility**

b(4)

This is acceptable by the reviewer

2. Sponsor's proposed labeling on pregnancy

b(4)

Reviewer's recommended changes:
Pregnancy
Pregnancy Category C. Safety in pregnant women has not been established. There are no adequate and well controlled studies of cosyntropin in pregnant women. Cosyntropin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

3. Sponsor's proposed labeling on nursing mothers

b(4)

Reviewer's recommended changes:
Nursing Mothers
It is not known whether cosyntropin is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cosyntropin, caution should be exercised when cosyntropin injection is administered to a nursing woman.

Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/lubas/weber
Review code: AP
File name: nda22028/000 (cosyntropin)

APPEARS THIS WAY
ON ORIGINAL

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/s/

Indra Antonipillai
10/3/2006 08:02:32 AM
PHARMACOLOGIST
From the pharm/tox point of view this application is recommended for approval, pending labeling changes.
This application is recommended for approval pending labeling changes

Karen Davis-Bruno
10/3/2006 09:00:24 AM
PHARMACOLOGIST

Signed off in DFS on 4/4/2006

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 22-028: This NDA is a 505(b)(2) application.
Submission date: 2/3/06
Sponsor: Sandoz Inc., Broomfield, CO.
Drug: Cosyntropin intravenous injection, 0.25 mg/ml

Introduction: Cosyntropin (Tetracosactide or α^{1-24} corticotropin) is a synthetic subunit of adrenocorticotropic hormone (ACTH). It is an open polypeptide chain containing the first 24 of the 39 amino acids of natural ACTH. Its intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency.

ITEM: NDA 22-028	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc)?	Yes		No new pharm/tox data have been provided. Sponsor refers to the previously marketed cortrosyn injection (NDA 16-750), and has provided brief summary of pharmacology and some published literature references.

4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical review? No carcinogenicity or other preclinical studies have been conducted with the current drug, since the reference listed drug (RLD) has been marketed since 1970 under NDA 16-750 in a lyophilized powder form. No animal studies were required for previously approved cortrosyn because it is a synthetic form of beta 1-24 corticotropin present in the natural product. This drug is also marketed as Synacthen in Europe as an injectable solution. The only difference between the current drug (cosyntropin) vs the previous marketed RLD cortrosyn is that the current drug is in aqueous solution (like the European synacthen) and does not require ——— (vs the USA marketed one which is in a powder form and requires ———

b(4)

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			No non-clinical studies have been conducted under this NDA 22-028

6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		The current aqueous solution form of the drug (cosyntropin) is basically similar to Cortrosyn, (the lyophilized powder form, NDA 16-750), except the current drug does not need _____. Therefore the formulation of the current drug is slightly different from the RLD. b(4) In the pre-NDA meeting, the current sponsor (Sandoz on 9/22/04, under IND 69,720) had posed a following question for us 'Can the requirements to supply information on clinical, pharmacology and toxicology supported by published literature suffice for a 505(b)2 application'?. Our response was that this is dependent upon the quantification of the impurity profile. Novel impurities or an impurity profile significantly different from the reference product may necessitate bridging toxicity studies'. However, no bridging studies have been provided. Sponsor states that both LC/MS methods were used to quantify the impurities in API and finished products of cosyntropin and cortrosyn (RLD). The results demonstrate that similar impurity profiles were observed with respect to unidentified impurities, and in fact the _____ (a known potential degradation product) is higher in the RLD than in the API of the Sandoz drug. Thus there is no added risk in the current product vs the marketed products. b(4) The chemist on this NDA has stated that the impurity profiles of these 2 products i.e marketed cortrosyn and the current cosyntropin (NDA 22-028) are similar but not the same. The impurity profiles of 2 peptides made by different _____ manufacturing processes can never be exactly the same. However, the similarity of impurity profiles of these 2 products should be adequate to support the filing of the new NDA as a 505(b)(2). b(4)

7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration of the approved RLD (cortosyn NDA 16-720) is im and iv. The route of administration of the current drug (cosyntropin) is iv (but not im) in humans.
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is in accordance with CFR. However, no carcinogenicity, mutagenicity, impairment of fertility, or repro-tox studies have been conducted with this drug under current or previous NDA. The label states that a study in rats noted inhibition of reproductive function like natural ACTH. Sponsor states that this drug is a synthetic subunit of ACTH, and the pharmacologic profile of cosyntropin or cortrosyn is similar to the that of purified natural ACTH. The 0.25 mg of cosyntropin will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH, and this product is used as a diagnostic agent in screening of patients presumed to have adrenocortical insufficiency. This drug is listed as pregnancy category C, as animal studies have not been conducted with cosyntropin or cortrosyn. Therefore, no data which express human dose multiples in mg/m^2 have been described.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		

10) Reasons for refusal to file: Not applicable

Reviewing Pharmacologist: Indra Antonipillai, DMEP
Supervisory Pharmacologist: Karen Davis-Bruno
File name: 22028-filing.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
4/4/2006 08:10:33 AM
PHARMACOLOGIST
From the pharm/tox point of view this application is filable.
From the pharm/tox point of view, this application is filable.

Karen Davis-Bruno
4/4/2006 08:21:39 AM
PHARMACOLOGIST