

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COSYNTROPIN safely and effectively. See full prescribing information for COSYNTROPIN.

**COSYNTROPIN injection, for intravenous use**

**Initial U.S. Approval: 2008**

### INDICATIONS AND USAGE

Cosyntropin injection is an adrenocorticotrophic hormone analog intended for use as a diagnostic drug in the screening of patients presumed to have adrenocortical insufficiency. (1)

### DOSAGE AND ADMINISTRATION

- Administer Cosyntropin injection as an intravenous injection (2.1)
- Collect baseline blood sample of 6 mL-7 mL just prior to injection (2.1)
- Add Cosyntropin injection to 2 mL to 5 mL of 0.9 % Sodium Chloride Injection and administer over a 2-minute period (2.1)
- Collect a second blood sample 30 minutes and/or 60 minutes later (2.1)
- Adult Dosage: 0.25 mg (2.2)
- Pediatric Dosage (0 to 2 years of age): 0.125 mg (2.3)
- Stimulated plasma cortisol levels of less than 18 mcg/dL-20 mcg/dL at 30 or 60 minutes post-injection are suggestive of adrenocortical insufficiency (2.4)

### DOSAGE FORMS AND STRENGTHS

- Injection, 0.25 mg/mL of Cosyntropin in 1 mL single-dose vial (3)

### CONTRAINDICATIONS

- Hypersensitivity reaction to cosyntropin injection, synthetic ACTH, or to any of the excipients (4)

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### WARNINGS AND PRECAUTIONS

- *Hypersensitivity*: reactions including anaphylaxis are possible. Monitor patients for hypersensitivity reactions and treat as needed. (5.1)
- *Diagnostic Inaccuracies*: Accuracy of diagnosis can be complicated by concomitant medications taken by the patient. Any condition that elevates or lowers cortisol binding globulin levels may increase or decrease plasma total cortisol levels, respectively. (2.1,5.2,7)

### ADVERSE REACTIONS

- Most common adverse reactions are anaphylactic reaction, bradycardia, tachycardia, hypertension, peripheral edema, and rash (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- *Drug effects on plasma cortisol levels*:
  - Cortisone or hydrocortisone: May elevate or lower plasma cortisol levels. Omit patient's pre-test dose on test day (7)
  - Synthetic glucocorticoids (oral, inhaled, or injectable): May lower plasma cortisol levels (7)
  - Spironolactone: May elevate plasma cortisol levels. Omit patient's pre-test dose on test day (7)
  - Estrogen: May elevate plasma total cortisol levels. Stop estrogen containing drugs 4 to 6 weeks prior to test (7)

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Cosyntropin injection is intended for use as a diagnostic drug in the screening of patients presumed to have adrenocortical insufficiency.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Administration Information

- Cosyntropin injection may be administered as an inpatient or outpatient procedure.
- Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing [see *Warnings and Precautions* (5.2)].
- Visually inspect Cosyntropin injection for particulate matter or discoloration prior to administration. Only use if the solution is clear and colorless.
- Collect a baseline blood sample of 6 mL to 7 mL just prior to injection.

- Add Cosyntropin injection to 2 mL to 5 mL of 0.9 % Sodium Chloride Injection and administer by intravenous injection over a 2-minute period.
- Collect a second blood sample 30 minutes and/or 60 minutes later.
- Discard any unused portion.
- Do not administer Cosyntropin injection intramuscularly.

## 2.2 Adult Dosage

The adult dose of Cosyntropin injection is 0.25 mg administered intravenously.

## 2.3 Pediatric Dosage

In pediatric patients, 0 to 2 years of age, a dose of 0.125 mg can be used.

## 2.4 Interpretation of Plasma Cortisol Levels after Cosyntropin Injection

Stimulated plasma cortisol levels of less than 18-20 mcg/dL at 30 or 60 minutes post-Cosyntropin injection are suggestive of adrenocortical insufficiency. Test results can be affected by concomitant medications and certain medical conditions [see *Warnings and Precautions (5.2)*].

## 3 DOSAGE FORMS AND STRENGTHS

Cosyntropin injection 0.25 mg/mL is a clear, colorless solution in a 1 mL single-dose vial.

## 4 CONTRAINDICATIONS

Hypersensitivity to Cosyntropin injection, synthetic ACTH, or to any of the excipients.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity to Cosyntropin Injection

Cosyntropin injection hypersensitivity reactions including anaphylaxis have been reported. Monitor patients for hypersensitivity reactions and treat as needed.

### 5.2 Diagnostic Inaccuracies

Accuracy of diagnosis can be complicated by concomitant medications taken by the patient. Cortisone or hydrocortisone use might falsely elevate or, in a paradoxical response, lower plasma cortisol levels. Spironolactone use may result in falsely elevated cortisol levels. Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing [see *Dosage and Administration (2.1)* and *Drug Interactions (7)*].

Use of synthetic glucocorticoid preparations (oral, inhaled, or injectable) might suppress plasma cortisol levels [see *Drug Interactions (7)*].

Use of estrogen containing drugs increases cortisol binding globulin levels which can elevate plasma total cortisol levels. To ensure accuracy of plasma total cortisol levels, discontinue estrogen containing drugs 4 to 6 weeks prior to testing to allow cortisol binding globulin levels to return to levels within the reference range [see *Dosage and Administration (2.1)* and *Drug Interactions (7)*]. Alternatively, concomitant measurement of cortisol binding globulin at the time of testing can be done; if cortisol binding globulin levels are elevated, plasma total cortisol levels are considered inaccurate.

Any condition that elevates or lowers cortisol binding globulin levels may increase or decrease plasma total cortisol levels, respectively. For example, cortisol binding globulin levels can be low in cirrhosis or nephrotic syndrome.

Measurement of cortisol binding globulin levels is recommended to ensure accuracy of interpretation of plasma total cortisol levels.

## 6 ADVERSE REACTIONS

The following adverse reactions have been identified during post approval use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- anaphylactic reaction
- bradycardia
- tachycardia
- hypertension
- peripheral edema
- rash

## 7 DRUG INTERACTIONS

**Drug effects on plasma cortisol levels [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.2)*]**

Accuracy of diagnosis can be complicated by concomitant medications taken by the patient including:

- Cortisone or hydrocortisone: May elevate or lower plasma cortisol levels. Omit patient's pre-test dose on the day of testing.
- Synthetic glucocorticoids (oral, inhaled, or injectable): May lower plasma cortisol levels.
- Spironolactone: May elevate plasma cortisol levels. Omit patient's pre-test dose on the day of testing.
- Estrogen: May elevate plasma total cortisol levels. Discontinue estrogen containing drugs 4 to 6 weeks prior to testing to allow cortisol binding globulin levels to return to levels within the reference range. Alternatively, concomitant measurement of cortisol binding globulin at the time of testing can be done; if cortisol binding globulin levels are elevated, plasma total cortisol levels are considered inaccurate.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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.

### 8.3 Nursing Mothers

It is not known whether cosyntropin is excreted into human 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.

## 11 DESCRIPTION

Cosyntropin, an adrenocorticotrophic hormone analog for intravenous use, is  $\alpha$  1-24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide with a molecular weight of 2933.44 containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The molecular formula of Cosyntropin is  $C_{136}H_{210}N_{40}O_{31}S$ . Its amino acid sequence is as follows:

Ser -	Tyr -	Ser -	Met -	Glu -	His -	Phe -	Arg -	Trp -	Gly -	Lys -	Pro -
1	2	3	4	5	6	7	8	9	10	11	12
Val -	Gly -	Lys -	Lys -	Arg -	Arg -	Pro -	Val -	Lys -	Val -	Tyr -	Pro
13	14	15	16	17	18	19	20	21	22	23	24

Cosyntropin injection is a 1 mL sterile solution in single-dose vials containing 0.25 mg of cosyntropin, 0.82 mg sodium acetate trihydrate, 6.4 mg sodium chloride, 10 mg mannitol, 1 mg glacial acetic acid, and water for injection, USP. Cosyntropin injection is a clear, colorless solution with a pH between 3.8 and 4.5.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Cosyntropin injection exhibits the full corticosteroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1-20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of cosyntropin injection is similar to that of purified natural ACTH. It has been established that 0.25 mg of cosyntropin injection will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of cosyntropin injection will produce maximal secretion of 17-OH corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids.

### 12.2 Pharmacodynamics

The extra-adrenal effects which natural ACTH and cosyntropin injection have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

In a study in normal volunteers, plasma cortisol levels peaked about  $2.5 \pm 0.5$  hours after intravenous injection of Cosyntropin and returned to baseline values by 6 hours.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Cosyntropin injection is supplied in a single-dose amber vial containing 1 mL of clear, colorless, sterile solution.

NDC 0781-3052-95 Cosyntropin injection 0.25 mg/mL, Box of 10 - 1 mL single-dose vials

Store refrigerated between 2° to 8°C (36° to 46°F). Protect from light. Protect from freezing.

Cosyntropin injection is intended as a single dose injection and contains no antimicrobial preservative. Any unused portion should be discarded.

## 17 PATIENT COUNSELING INFORMATION

*Hypersensitivity reactions:* Inform patients that hypersensitivity reactions can occur with Cosyntropin injection.

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