Licensing Requirements

MP BIOMEDICALS, LLC is permitted to transfer radioactive materials only after the receipt of a copy of the customer's Radioisotope License. In emergency situations, the purchaser may furnish oral certification of the above information provided a copy of the license is received by MP Biomedicals within ten (10) days.

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ORDER TODAY by CALLING MP Biomedicals Customer Service Department in Irvine, California.

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ImmuChem™ 17α-HYDROXYPROGESTERONE DA CATALOG No. 07-171102 (100 Tubes)

European Authorized Representative:
MP Biomedicals Europe, n.v.-s.a.
Doornveld 10
B-1731 Asse-Relegem, Belgium
Tel: +32 2 466 0000 / Fax: +32 2 466 2642

I. INTRODUCTION

A. INTENDED USE

The ImmuChem™ 17α-Hydroxyprogesterone assay is intended to detect and measure this steroid in unextracted serum or plasma of adults and children. The steroid 17α-hydroxyprogesterone (17-OH-P) is produced by both the adrenal cortex and gonads. Even though 17-OH-P has relatively little progestational activity, it is of intense clinical interest because it is the immediate precursor to 11-desoxycorticisol (Cpd-S). Because Cpd-S is produced by 21-hydroxylation of 17-OH-P, measurement of 17-OH-P is a useful indirect indicator of 21-hydroxylase activity. In congenital 21-hydroxylase deficiency, the most common variety of congenital adrenal hyperplasia (CAH), 17-OH-P is secreted in abundant excess. It is moderately elevated in the 11β-hydroxylase deficiency as well. Measurement of 17-OH-P is therefore valuable in the initial diagnosis of CAH.

B. CLINICAL PHYSIOLOGY

1. Adult non-pregnant women:

   In adult non-pregnant women in the childbearing age group, 17-OH-P concentrations vary over the menstrual cycle with luteal phase concentrations being higher than follicular phase concentrations. [1] This is because 17-OH-P is secreted parallel with progesterone from maturing follicles or from the corpus luteum. [1] There is also a diurnal variation of 17-OH-P concentrations. This rhythm is parallel with adrenal cortisols secretion such that maximum 17-OH-P concentrations are measured in samples obtained between midnight and 8:00 a.m. [2]

2. Adult males:

   There is little information available on the systemic variability of 17-OH-P concentrations in adult males. [1]

3. Pregnant women and newborn children:

   The steroid 17-OH-P is produced in large amounts by the fetus and the adrenals. It is secreted in abundance into both the fetal and maternal circulation. The maternal concentrations of 17-OH-P increase very sharply after 32 weeks gestational age to about 4-fold above basal concentrations at term. [3]

C. CLINICAL APPLICATIONS

1. Congenital adrenal hyperplasia:

   The principle application of the 17-OH-P RIA is in the diagnosis of CAH in newborns with ambiguous genitalia and in virilized adolescent girls. [4] Since 17-OH-P is the immediate precursor to 11-desoxycorticisol, basal 17-OH-P concentrations are sharply elevated in patients with 21-hydroxylase deficiency and to a lesser degree in patients with 11-hydroxylase deficiency. Because 17-OH-P concentrations are so markedly elevated in newborns and adolescent girls afflicted with CAH, a single basal measurement is all that is normally required to make the diagnosis. [4,5]

2. Late onset adrenal hyperplasia:

   More recently, 17-OH-P concentrations have been utilized in the evaluation of androgenized women where late onset 21-hydroxylase deficiency is suspected. This condition is clinically very subtle and since the presentation is the same as classical polycystic ovarian disease [4, 6-8], basal plasma 17-OH-P concentrations, unlike classical congenital adrenal hyperplasia, are normal. The diagnosis is made by administration of an ACTH stimulation test. [2, 6-8]

3. Other applications:

   Measurement of 17-OH-P concentrations is also utilized in evaluation of both men and women with acne vulgaris, male pattern baldness and in some subtle forms of infertility. [7] Experience with these applications is limited.

II. PRINCIPLE OF THE TEST

Radioimmunoassay (RIA) is the term applied to the measurement of the concentration of antigen molecules using a radioactive label that quantitates the amount of antigen (i.e., hormone) by determination of the extent to which it combines with its antibody.

In the assay, a limited amount of specific antibody (Ab) is reacted with the corresponding hormone ("H") labeled with a radioisotope. Upon addition of an increasing amount of the hormone (H), a correspondingly decreasing fraction of "H added is bound to the antibody. After separation of the bound from the free "H by various means, the amount of radioactivity in one or both of these two fractions is evaluated and used to construct a standard curve against which the unknown samples are measured.

III. REAGENTS PROVIDED AND LABEL COLOR CODE (100 Tube Kit)

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>LABEL COLOR BAR</th>
<th>VOLUME OR QUANTITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid Diluent</td>
<td>Tan</td>
<td>5.5 mL</td>
</tr>
<tr>
<td>Cat. No. 07-166191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-17-OH-P</td>
<td>Yellow</td>
<td>52 mL</td>
</tr>
<tr>
<td>Cat. No. 07-171113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-OH-P Standards (7)</td>
<td>Green</td>
<td>0.5 mL ea*</td>
</tr>
<tr>
<td>Cat. No. 07-171130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precipitant Solution</td>
<td>Red</td>
<td>52 mL</td>
</tr>
<tr>
<td>Cat. No. 07-166624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-OH-P 125</td>
<td>Blue</td>
<td>52 mL</td>
</tr>
<tr>
<td>Cat. No. 07-171121</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*0 ng/mL standard contains 1.0 mL.
II. REAGENT DESCRIPTION (FOR IN-VITRO DIAGNOSTIC USE ONLY)

A. STEROID DILUENT

Phosphosaline gelatin buffer (pH 7.0) containing rabbit gamma globulins.

STORAGE: 2 to 8°C.
STABILITY: Refer to expiration date on kit vial.

B. ANTI-17α-HYDROXYPROGESTERONE ANTI

17α-Hydroxyprogesterone-7α- CETE-BSA was used as the immunogen to generate antiserum in rabbits. The antiserum is titered to bind 35-60% of the 17-OH-P\(^{125}I\) in the absence of nonradioactive 17-OH-P.

STORAGE: 2 to 8°C.
STABILITY: Refer to expiration date on kit vial.

C. 17α-HYDROXYPROGESTERONE STANDARDS

Seven standards are provided at the following concentrations: 0, 0.1, 0.25, 1.0, 2.5, 10 and 25 ng/mL. The standards have been prepared in a BSA buffer solution.

STORAGE: 2 to 8°C.
STABILITY: Refer to expiration date on kit vial.

D. PRECIPITANT SOLUTION

This is a mixture of PEG and goat anti-rabbit gamma globulins contained in phosphosaline buffer. 0.5 mL of this precipitant will immediately precipitate all the antibody bound antigen.

STORAGE: 2 to 8°C.
STABILITY: Refer to expiration date on kit vial.

E. 17α-HYDROXYPROGESTERONE-\(^{125}I\) TRACER

This radioactive material contains less than 3 µCi per vial for a 100 tube kit on the date of shipment. 0.5 mL of this radioactive material will provide approximately 40,000 cpm at 75% counter efficiency on the date of shipment.

STORAGE: 2 to 8°C.
STABILITY: Refer to expiration date on kit vial.

V. LIMITATIONS, PRECAUTIONS AND GENERAL COMMENTS

NOTE: These reagents contain sodium azide which has a tendency to build up in lead or copper plumbing forming potentially explosive metal azides. Always flush large quantities of water through the plumbing after the disposal of these reagents. It is recommended to dispose of radioactive waste according to the established U.S. NRC guidelines.

A. Strict adherence to the protocol is recommended. Any changes are done at the discretion of the user.
B. Care must be taken that clinical samples contain no exogenous radioactivity, since its presence may lead to erroneous results.
C. A standard curve must be established for every assay run.
D. The reagents provided in this kit are intended only for the specific quantitation of serum or plasma 17-OH-P in humans. Any other uses, such as animal research, should be independently determined by the user.
E. The kit reagents and materials are intended for use as an integral unit. Do not mix various lots of any component reagent within an individual run.
F. Extractions must be performed on neonatal, blood-spot and third trimester pregnancy samples.
G. The use of grossly hemolyzed or lipemic samples should be avoided.
H. The reagents supplied in this kit are for IN-VITRO DIAGNOSTIC USE.
I. RADIOACTIVE MATERIALS

Please observe the following precautions when handling this radioactive material:
1. This radioactive material may be received, acquired, possessed, and used only by physicians, clinical labs, or hospitals, and only in in-vitro clinical or laboratory tests not involving internal or external administration of the materials, thus the radiation therein, to humans or animals. Its receipt, acquisition, possession, use and transfer are subject to the regulations of, and with a general license from, the U.S. NRC or the State with which the U.S. NRC has entered into agreement for the exercise of regulatory authority.
2. Immediately upon receipt of this kit, check for breakage and verify contents as per the packing list. Should there be breakage or questions regarding this kit's contents, immediately notify your representative.
3. Kit reagents should be stored and used only at clean, designated work stations of the laboratory. Although exposure to radiation from the small amount of radioactive material supplied is negligible, it is good practice to designate a storage area at least 10 feet from any work station, if practical. Furthermore, persons under the age of 18 should not be permitted to handle radioactive material or enter into an area where it is either stored or used.
4. Should there be spillage of any radioactive material, the following clean-up procedure is recommended: blot spillage with absorbent material while leaving the laboratory area.
5. The pipetting of radioactive material by mouth should not be permitted. Smoking, eating, or drinking while performing tests involving radioactive material should not be permitted. Lastly, persons handling radioactive material should wash their hands immediately after handling and prior to leaving the laboratory area.
6. Absorbent paper for blotting.

VI. SPECIMEN COLLECTION AND HANDLING

Plasma - Draw blood into a green capped (heparin) Vacutainer™ tube. After separation, store the plasma in a refrigerator (can be stored for up to one week) or store frozen.
Serum - Draw blood into a red capped Vacutainer™ tube. Allow the blood to clot for at least thirty minutes at room temperature. Separate the serum and store under the same conditions as the plasma.

Neonatal Blood - Refer to reference #5.

Capillary Whole Blood - Refer to Becton Dickinson microcapillary whole blood collection system (Becton Dickinson and Company, Rutherford, New Jersey 07070).

VII. EQUIPMENT AND REAGENTS REQUIRED

In addition to the reagents supplied with the kit, the following materials are required:
1. Pipettor and/or pipets that can accurately and precisely deliver the required volumes (10 µL and 500 µL).
2. Gamma counter.
3. Laboratory vortex mixer.
4. Test tube rack.
5. Centrifuge-refrigerated (preferred) capable of 2300-2500 rpm (1000 x g).
6. 10 x 75 mm tubes for RIA.
7. Absorbent paper for blotting.

*Available from MP BIOMEDICALS

VIII. ASSAY PROCEDURE

A. ASSAY PREPARATIONS

1. Bring the reagents to room temperature prior to use.
2. Set up assay in consecutively numbered 10x75 mm disposable glass test tubes.

B. ASSAY STEPS

1. Add 0.5 mL of STEROID DILUENT to tubes number 1 and 2.
2. Add 10 µL of the 0.0 ng/mL STANDARD to tubes number 1, 2, 3, and 4.
3. Add 10 µL of each 17-OH-P STANDARD (0.1-25 ng/mL) to tubes 5-16.
4. *Add 10 µL of control serum or patient’s serum or plasma to tubes number 17 to end of assay.
5. With the EXCEPTION OF TUBES NUMBER 1 AND 2, add 0.5 mL of ANTI-17-OH-P to all the tubes.
6. Vortex mix and incubate at room temperature for 60 minutes. NOTE THAT THIS INCUBATION PERIOD IS WITHOUT 17-OH-P\(^{125}I\).
7. Add 0.5 mL of 17-OH-P\(^{125}I\) to all the tubes.
8. Vortex mix and incubate at ROOM TEMPERATURE for another 60 minutes.
9. After incubation, add 0.5 mL of PRECIPITANT SOLUTION to all the tubes. Vortex mix thoroughly.
10. Centrifuge all the assay tubes at 2300-2500 rpm (1000 x g) for 20 minutes. Aspirate or decant the supernatant. (If decanting, blot the rim of test tubes on absorbent paper before turning right side up.)
11. Count the precipitate in a gamma counter.

*IMPORTANT NOTICE: For suspected CAH samples, dilute 1:100 with normal saline (use 10 µL of this dilution in assay and multiply the value read off the standard curve times 100).

C. QUALITY CONTROL

Serum pools or commercially available controls containing a low, normal, and high concentration of 17α-hydroxyprogesterone should be assayed routinely as unknowns. The concentrations of these controls should be plotted on a run to run basis using a Levy-Jennings type system in order to assess the performance and reliability of the assay. For further information, see: DAVID RODBARD: “Statistical Quality Control and Routine Data Processing for Radioimmunoassays and Immunoassay Radiometric Assays.” CLIN CHEM 20/10, 1255-1270 (1974).
X. PROTOCOL

A. Take the average counts of all duplicate tubes (samples and standards). Subtract the non-specific binding counts from the averages obtained above. This yields the corrected counts. Divide the corrected counts by the corrected zero standard counts to obtain the percent bound (B/Bo).

B. Formula:

\[
\%B/Bo = \frac{\text{CPM (sample) – CPM (NSB)}}{\text{CPM (0 Standard) – CPM (NSB)}} \times 100
\]

CPM = Average counts of duplicates.
NSB = Non-specific binding tube.
0 Standard = 0 ng/mL tube (also known as the 100% binding tube).

C. Construct a plot of percent bound versus the concentration of the 17-OH-P standards starting with the 0.1 ng/mL point. Either log-logit or semi-log paper may be used. This yields the standard curve.

D. Using the standard curve, determine the 17-OH-P concentration for each sample.

E. Although the standard curve is linear on a log-logit system, it is erroneous to extrapolate a value for a patient sample that binds either higher or lower than the standard curve.

XI. SAMPLE ASSAY

These calculations are for example only. The user must construct a standard curve each time the assay is run.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>CPM</th>
<th>AVG. CPM</th>
<th>AVG.-NSB CPM</th>
<th>%B /Bo 17OH-P (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSB (blank)</td>
<td>1543</td>
<td>1388</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 ng/mL</td>
<td>16715</td>
<td>17293</td>
<td>17004</td>
<td>15616</td>
</tr>
<tr>
<td>0.1 ng/mL</td>
<td>16025</td>
<td>15549</td>
<td>15787</td>
<td>14399</td>
</tr>
<tr>
<td>0.25 ng/mL</td>
<td>13320</td>
<td>13489</td>
<td>13404</td>
<td>12016</td>
</tr>
<tr>
<td>1.0 ng/mL</td>
<td>8822</td>
<td>9082</td>
<td>8952</td>
<td>7564</td>
</tr>
<tr>
<td>2.5 ng/mL</td>
<td>6484</td>
<td>6553</td>
<td>6528</td>
<td>5140</td>
</tr>
<tr>
<td>10 ng/mL</td>
<td>4172</td>
<td>3850</td>
<td>4011</td>
<td>2623</td>
</tr>
<tr>
<td>25 ng/mL</td>
<td>2625</td>
<td>3045</td>
<td>2835</td>
<td>1447</td>
</tr>
<tr>
<td>Control 1</td>
<td>15037</td>
<td>15378</td>
<td>15207</td>
<td>13819</td>
</tr>
<tr>
<td>Control 2</td>
<td>11425</td>
<td>11421</td>
<td>11423</td>
<td>10035</td>
</tr>
<tr>
<td>Control 3</td>
<td>5854</td>
<td>5979</td>
<td>5916</td>
<td>4528</td>
</tr>
</tbody>
</table>

XII. SAMPLE STANDARD CURVE

NOTE: This curve serves only as an example. Patient sample values must not be derived from it.

XIII. EXPECTED NORMAL VALUES

A. Reproductive aged women

Follicular phase [1]: 0.10 – 0.80 ng/mL
Luteal phase [1]: 0.27 – 2.90 ng/mL
Post ACTH [2]: < 3.2 ng/mL

B. Normal men [1]: 0.31 – 2.17 ng/mL

C. Third trimester pregnant women and newborns*

Pregnant women [3]: 2.0 – 12.0 ng/mL
Newborn [3] (capillary plasma): < 0.7 – 2.5 ng/mL

*NOTE: These samples require an extraction step prior to assaying.

As with any diagnostic test, differences in physiological ranges may be encountered from laboratory to laboratory due to patient demographics, laboratory techniques, and population sampling. These ranges should only be used as a guideline. We recommend each laboratory establish its own ranges using a statistically significant number of characterized patient specimens in each diagnostic category.

XIV. PERFORMANCE CHARACTERISTICS

A. PARALLELISM (linearity of dilutions)

Patient samples were diluted as indicated using the 0 ng/mL standard.

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>NEAT (ng/mL)</th>
<th>1:2 (ng/mL)</th>
<th>1:4 (ng/mL)</th>
<th>1:8 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4.0</td>
<td>1.9 x 2=3.8</td>
<td>1.1 x 4=4.4</td>
<td>0.55 x 8=4.4</td>
</tr>
<tr>
<td>2.</td>
<td>4.5</td>
<td>2.2 x 2=4.4</td>
<td>1.1 x 4=4.4</td>
<td>0.64 x 8=5.1</td>
</tr>
<tr>
<td>3.</td>
<td>5.5</td>
<td>2.8 x 2=5.6</td>
<td>1.4 x 4=5.6</td>
<td>0.84 x 8=6.7</td>
</tr>
<tr>
<td>4.</td>
<td>3.7</td>
<td>2.0 x 2=4.0</td>
<td>1.0 x 4=4.0</td>
<td>0.61 x 8=4.9</td>
</tr>
</tbody>
</table>

Average 94%

B. RECOVERY

To demonstrate the accuracy of the direct 17-OH-P\(^{125}\I method, known amounts of 17-OH-P were added to aliquots of two serum samples.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Actual 17-OH-P Conc. (ng/mL)</th>
<th>17-OH-P Added (ng/mL)</th>
<th>17-OH-P Expected (ng/mL)</th>
<th>17-OH-P Obtained (ng/mL)</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.46</td>
<td>0.97</td>
<td>1.43</td>
<td>1.3</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>2.96</td>
<td>2.4</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.7</td>
<td>5.16</td>
<td>4.7</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>7.76</td>
<td>7.2</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>11.00</td>
<td>10.2</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>94%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>0.49</td>
<td>0.97</td>
<td>1.46</td>
<td>1.6</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>2.39</td>
<td>2.7</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.7</td>
<td>5.19</td>
<td>5.7</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.3</td>
<td>7.79</td>
<td>7.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>11.00</td>
<td>11.3</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>107%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: These samples require an extraction step prior to assaying.

As with any diagnostic test, differences in physiological ranges may be encountered from laboratory to laboratory due to patient demographics, laboratory techniques, and population sampling. These ranges should only be used as a guideline. We recommend each laboratory establish its own ranges using a statistically significant number of characterized patient specimens in each diagnostic category.
C. PATIENT SAMPLE CORRELATION

Seventy patient samples were analyzed in triplicate using the ImmuChem™ 17α-Hydroxyprogesterone assay and a commercial method. The results are shown below:

D. INTRA-ASSAY VARIATION (n=10)

<table>
<thead>
<tr>
<th>Control 1</th>
<th>Control 2</th>
<th>Control 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.48</td>
<td>2.32</td>
<td>14.7</td>
</tr>
<tr>
<td>0.56</td>
<td>2.01</td>
<td>14.1</td>
</tr>
<tr>
<td>0.57</td>
<td>2.12</td>
<td>12.7</td>
</tr>
<tr>
<td>0.51</td>
<td>1.99</td>
<td>14.6</td>
</tr>
<tr>
<td>0.47</td>
<td>1.99</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Mean = 0.52 2.06 14.2
S.D. = 0.033 0.116 1.28
C.V. = 6.5% 5.6% 9.0%

E. INTER-ASSAY VARIATION (n=20)

<table>
<thead>
<tr>
<th>Control 1</th>
<th>Control 2</th>
<th>Control 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.57</td>
<td>2.3</td>
<td>15.5</td>
</tr>
<tr>
<td>0.56</td>
<td>2.2</td>
<td>16.6</td>
</tr>
<tr>
<td>0.55</td>
<td>2.7</td>
<td>19.3</td>
</tr>
<tr>
<td>0.56</td>
<td>2.1</td>
<td>19.7</td>
</tr>
<tr>
<td>0.54</td>
<td>2.3</td>
<td>15.7</td>
</tr>
<tr>
<td>0.60</td>
<td>2.6</td>
<td>17.6</td>
</tr>
<tr>
<td>0.57</td>
<td>2.6</td>
<td>20.4</td>
</tr>
<tr>
<td>0.49</td>
<td>2.0</td>
<td>13.8</td>
</tr>
<tr>
<td>0.52</td>
<td>2.2</td>
<td>14.3</td>
</tr>
<tr>
<td>0.45</td>
<td>2.0</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Mean = 0.54 2.3 16.2
S.D. = 0.04 0.23 2.3
C.V. = 7.4% 10.0% 14.2%

F. MINIMUM DETECTABLE DOSE

Twenty (20) duplicates of the zero standard were set up in an assay to determine the minimum quantity of 17α-Hydroxyprogesterone detectable by this assay. By subtracting two standard deviations from the mean of the zero tubes, we find the minimum detectable dose of 17α-Hydroxyprogesterone in this system to be 0.08 ng/mL.

X. SPECIFICITY OF THE ANTISERUM

The following materials have been checked for cross-reactivity. The percentages indicate cross reactivity at 50% displacement compared to 17α-Hydroxyprogesterone.

<table>
<thead>
<tr>
<th>STEROIDS</th>
<th>% CROSS REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-Hydroxyprogesterone</td>
<td>100.0</td>
</tr>
<tr>
<td>17α-Hydroxypregnenolone</td>
<td>3.7</td>
</tr>
<tr>
<td>11-Desoxycorticisol</td>
<td>2.6</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.7</td>
</tr>
</tbody>
</table>

XVI. REFERENCES