

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k061886

B. Purpose for Submission:

New device

C. Measurand:

Insulin-like growth factor binding protein-1 (IGFBP-1)

D. Type of Test:

Qualitative

E. Applicant:

Medix Biochemica

F. Proprietary and Established Names:

Actim PROM and Actim PROM Controls

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1550

21 CFR 862.1660

21 CFR 862.9 (c)(9) Limitations of exemptions (For near patient testing (point of care))

2. Classification:

Class I

3. Product code:

OAM and JJX

4. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Actim PROM test is a visually interpreted, qualitative immunochromatographic rapid test for the detection of amniotic fluid in cervicovaginal secretions during pregnancy. Actim PROM test detects IGFBP-1, which is a major protein in amniotic fluid and a marker of the presence of amniotic fluid in a cervicovaginal sample. The test is intended for professional use to help diagnose the rupture of fetal membranes (ROM) in pregnant women at >34 weeks gestation when patients report signs, symptoms or complaints suggestive of ROM or if such signs are otherwise observed.

The Actim PROM Controls are intended for use as external controls with the Actim PROM test. The controls may also be used to demonstrate negative results and weak and strong positive results.

3. Special conditions for use statement(s):

The device is intended for use in point-of-care and clinical laboratory settings.

4. Special instrument requirements:

None are required.

I. Device Description:

Actim PROM is available in packages of 3, 10 and 20 tests. Each individual test pack contains a sterile polyester swab, specimen extraction solution (0.5 mL), and a dipstick in a sealed aluminum pouch. The extraction solution is phosphate buffer containing BSA, protease inhibitor and preservative. The dipstick contains two mouse monoclonal antibodies to human IGFBP-1 and BSA.

The Actim PROM Controls Kit contains the following items: 1 vial each of Actim PROM Negative Control, Actim PROM Positive Control (low), and Actim PROM Positive Control (high); Actim Reconstitution Solution (2 mL); and instructions for

use. The positive controls consist of human IGFBP-1 in a buffered protein solution with preservative. The negative control consists of the same matrix without added antigen. All controls are supplied lyophilized and are reconstituted with the Reconstitution Solution.

J. Substantial Equivalence Information:

1. Predicate device name(s):

AmniSure ROM (Rupture Of [fetal] Membranes) Test

2. Predicate 510(k) number(s):

k030849

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Indications for Use	Aid in detecting rupture of fetal membranes in pregnant women at >34 weeks gestation when patients report signs, symptoms or complaints suggestive of ROM or if such signs are otherwise observed.	Same
Specimen collection	Vaginal swab	Same
Principle	Immunochromatographic assay	Same

Differences		
Item	Device	Predicate
Analyte	Insulin-like growth factor binding protein-1 (IGFBP-1)	Placental alpha-1 microglobulin (PAMG-1)
External QC Materials	Negative, low positive, and high positive controls	Positive control

K. Standard/Guidance Document Referenced (if applicable):

None were referenced.

L. Test Principle:

The test principle is lateral flow immunochromatography.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Samples (control solutions in specimen extraction solution) containing six different IGFBP-1 concentration levels were evaluated for repeatability / intra-assay precision. The levels represented negative, weakly positive and strongly positive samples. The samples were tested with 10 replicates each during the same day using 3 different lots of the Actim PROM test. Repeatable results were obtained. These test results were consistent with the detection limit of the assay.

Samples (control solutions in specimen extraction solution) containing ten different IGFBP-1 concentration levels were evaluated for reproducibility / inter-assay precision. The levels represented negative, weakly positive and strongly positive samples. The samples were tested with 3 replicates each on 7 days using 3 different lots of the Actim PROM test. Reproducible results were obtained. These test results were consistent with the detection limit of the assay.

b. *Linearity/assay reportable range:*

The measuring range of the Actim PROM test is approximately 25 µg/L – 500,000 µg/L in an extracted sample.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The positive controls consist of purified human insulin-like growth factor binding protein-1 (IGFBP-1) with bovine serum albumin and preservative. The positive controls are prepared by adding hIGFBP-1 antigen to the negative control solution. The solutions are then adjusted to the following concentration ranges using IGFBP-1 quantitative ELISA: 40 µg/L (34-46 µg/L) for the low positive control and 250 µg/L (212-287 µg/L) for the high positive control.

The IGFBP-1 antigen in the Positive Controls has been shown to be negative for HBsAG, HIV type 1 and 2 antibodies, HCV and syphilis. However, such tests are unable to prove the complete absence of viruses, and therefore the controls should be treated as potentially infectious.

To test closed stability, controls are tested at the time of manufacture and after the designated storage times at the specified temperatures. For each time point, testing is performed with one lot of Actim PROM test using three

replicate dipsticks. The expected positive and negative results were obtained in all cases.

To test open stability, studies of the reconstituted controls were performed after 25 hours storage at three different temperatures (2-8°C, 25°C, and 30°C) and also after 4, 7, and 8 days storage at 2-8°C. For both studies, testing was performed with three lots of Actim PROM Controls and with three lots of Actim PROM tests. The expected positive and negative results were obtained in all cases and support the stated open stability of Actim PROM Controls.

d. Detection limit:

The analytical sensitivity was evaluated using specimens with 13 different concentrations of IGFBP-1 ranging from 0 µg/L – 500,000 µg/L. The samples were control solutions in Specimen Extraction Solution and were tested with 3 different lots of the Actim PROM test. With each lot, 10 replicates were tested at concentrations around the detection limit and 3 replicates were tested at higher concentrations. The analytical sensitivity or detection limit is approximately 25 µg/L of IGFBP-1 in extracted sample, which corresponds to approximately 400 µg/L in the unextracted sample.

e. Analytical specificity:

The analytical specificity (cross-reactivity) was tested with human IGFBP proteins at concentrations ranging from 10 - 5,000 µg/L of each protein in extracted sample. Additionally, control solutions containing 0 – 1,000 µg/L of human IGFBP-1 were tested. The samples were tested with 3 different lots using 3 replicates from each test. The results showed that the Actim PROM test is specific for IGFBP-1. No cross-reactivity was observed using human IGFBP-2, -3, -4, -5 and -6 proteins.

The effect of drugs, semen, whole blood, urine from pregnant women, shower and bath products, and other vaginal products were assessed for potential interference. Samples with and without drug preparations were collected and extracted into Specimen Extraction Solution containing 0 - 1,000 µg/L of IGFBP-1. Semen samples were collected and extracted into Specimen Extraction Solution containing 0 – 100 µg/L of IGFBP-1. Blood samples were spiked with 0 – 500 µg/L of IGFBP-1, corresponding to the concentration of blood in pregnant women, then extracted into Specimen Extraction Solution containing 0 and 50 µg/L of IGFBP-1. Urine samples (10) from pregnant women were collected and extracted into Specimen Extraction Solution containing 0 – 100 µg/L of IGFBP-1. Solutions (0.1%) of common shower and bath products were collected and extracted into Specimen Extraction Solution containing 0 and 50 µg/L of IGFBP-1. Five different concentrations each of other substances used in the vaginal area were

extracted into the Specimen Extraction Solution containing 0 and 100 µg/L of IGFBP-1.

Three different lots of Actim PROM were used for testing. The results were interpreted after 5 minutes. No interference of vaginal formulations, semen, whole blood, urine from pregnant women, and shower, bath, and other vaginal products with the performance of Actim PROM was observed.

f. Assay cut-off:

See detection limit above.

2. Comparison studies:

a. Method comparison with predicate device:

The performance of the Actim PROM test was evaluated in comparison with the predicate device. Vaginal secretions samples were collected from non-pregnant women and spiked with different concentrations of amniotic fluid. One hundred samples (100) were tested with both devices.

Test results for the subject device were reported as positive, negative, or indeterminate for very weak (trace) test lines. Test results for the predicate device were reported as positive or negative.

The samples contained various IGFBP-1 concentrations ranging from approximately 4 µg/L to approximately 6,000 µg/L. The percent agreement between the devices for the positive results was 80%. The percent agreement for the negative results was 100%. Overall agreement was 86%.

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

The sponsor provided published studies to support clinical performance of the Actim PROM in the hands of intended end users under the intended conditions of use.

In one study by Ragosch et al (1996), samples were collected from forty-four (44) cases of suspected rupture and thirty-one (31) with intact membranes for testing on the Actim PROM device. The gestational age of the patients was up to 41 weeks. Women with over 8 hours between the examination and membrane rupture, strong bleeding, or cerclage were excluded. Upon further examination, forty (40) were diagnosed as having intact membranes and thirty-five (35) as having ruptured membranes.

In another study by Jain and Morris (1998), samples were collected from patients with admission history of premature rupture of membranes (i.e., suspected rupture). One hundred (100) patients up to 42 weeks gestation were included. Women presenting with obvious flooding of amniotic fluid were excluded from the study. The final diagnosis of membrane status indicated that seventy-five (75) were intact and twenty-five (25) were ruptured.

The results from the two studies are as follows:

	N	Sensitivity Estimate	Specificity Estimate
Ragosch et al	75	35/35 = 100%	33/40 = 82.5%
Jain and Morris	100	25/25 = 100%	67/75 = 89%
Combined	175	60/60 = 100%	100/115 = 87%
95% CI		94% to 100%	79.4% to 92.5%
		PPV	NPV
Combined	175	60/75 = 80%	100/100 = 100%
95% CI		69% to 88%	96.4% to 100%

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The expected values were determined in literature studies. The IGFBP-1 concentration in amniotic fluid is between 10,500 and 350,000 µg/L (Rutanen et al. 1993).

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.