CPAL
Central Pennsylvania Alliance Laboratory

Technical Bulletin
No. 152

March 28, 2016

--IMPORTANT NOTICE--
Estradiol Assay
Interference from the Drug Fulvestrant (Faslodex®)

Contacts:

- ✓ Stephanie Frey, MT(ASCP) 717-812-4768
  Operations Manager, Clinical Pathology, CPAL

- ✓ Dr. Jennifer Thebo, PhD, MT(ASCP) 717-851-3210
  Director of Technical Operations and Scientific Affairs, CPAL

Effective Date: Immediately

Members should notify ordering providers of the following:
Estradiol immunoassays have been reported to demonstrate significant cross-reactivity with the drug fulvestrant (Faslodex®). This cross-reactivity can cause falsely elevated estradiol levels in patients being treated with fulvestrant. Abbott Diagnostics, the manufacturer of the estradiol assay used at CPAL, has confirmed the potential of falsely elevated estradiol results by spiking a sample (representative of post-menopausal females) with 25,100 pg/mL fulvestrant (representative Cmax for fulvestrant). Results of that experiment are shown below in Table 1.

Table 1: Investigation Results on the ARCHITECT ® i2000 System

Estradiol Result of Neat Sample pg/mL	Estradiol Result of Spiked Sample pg/mL	% Change (Interference)	% Cross Reactivity
29.14	85.80	194.44	0.23

% Change = (spiked sample result – neat sample result)/neat sample result x 100
% Cross Reactivity = (spiked sample result – neat sample result)/concentration of fulvestrant x 100

In CPAL's investigation of this report, we found that the manufacturer of the assay previously used at CPAL (Siemens Healthcare Diagnostics Immulite ® 2000) has also reported the potential for falsely elevated estradiol levels in patients being treated with fulvestrant. This effect has been confirmed with a study performed in a similar manner on the following Siemens immunoassay systems, using 20,000 pg/mL to spike samples: ADVIA Centaur ®, Dimension Vista ®, Immulite ® 1000, and Immulite ® 2000. See Table 2 for results of this study using the previous CPAL assay on the Immulite ® 2000.

Table 2: Investigation Results on the IMMULITE ® 2000 System

Estradiol Result of Neat Sample pg/mL	Estradiol Result of Spiked Sample pg/mL	% Change (Interference)	% Cross Reactivity
21.6	83.3	286.6	0.31
49.07	126.7	158.2	0.31
200.6	270.2	34.7	0.35

% Change = (spiked sample result – neat sample result)/neat sample result x 100
% Cross Reactivity = (spiked sample result – neat sample result)/concentration of fulvestrant x 100

There are also reports that Roche Diagnostics has issued a similar field safety notice for their estradiol II and estradiol III assays.

Effect of Tamoxifen on Estradiol:
A review of available literature indicates that tamoxifen does not interfere with the Abbott ARCHITECT ® estradiol assay that is currently in use at CPAL. Abbott states in the package insert that testing for cross-reactivity was performed using synthetic specimens containing essentially no residual estradiol. The specimens were spiked with tamoxifen at 183 ng/mL and no cross-reactivity was detected. They also spiked synthetic specimens containing 600 pg/mL of estradiol with 183 ng/mL of tamoxifen. Recovery of estradiol was 100.6%, indicating that no significant interference was detected. The level of tamoxifen used in these studies exceeds the Cmax for tamoxifen of 35-45 ng/mL following a single 20 mg dose.

Conclusions & Recommendations:
Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor (ER) in a competitive manner with an affinity that is comparable to estradiol. The drug is used in the treatment of ER-positive, tamoxifen-resistant breast cancer.

There is potential for any estradiol immunoassay to exhibit interference from fulvestrant. Therefore, it is recommended that fulvestrant-treated patients be tested with an assay that is likely to have negligible interference of this type. It is possible that Liquid Chromatography-Mass Spectrometry (LC-MS) assays may differentiate fulvestrant from estradiol. Quest Diagnostics offers the following assay:

Estradiol, Ultrasensitive, LC/MS/MS
Test Code: 30289 (Each laboratory should confirm the proper test code for their facility)

Tamoxifen, a drug with similar mode of action used to treat ER-positive breast cancer, does NOT exhibit interference with the ARCHITECT ® estradiol assay. The CPAL assay may be used for patients being treated with tamoxifen.

References:

1. Product Correction: ARCHITECT ® Estradiol Reagent. Abbott Ireland Diagnostics Division; March 2016
2. Berger D, Waheed S, Fattout Y, Kazlauskaite R, Usha L. *False Increase of Estradiol Levels in a 36-Year-Old Postmenopausal Patient With Estrogen Receptor-Positive Breast Cancer Treated With Fulvestrant.* Clinical Breast Cancer. 2016; 16(1), E11-E13.

3. Faslodex® FDA prescribing information: AstraZeneca Pharmaceuticals LP. Wilmington, DE; March 2016.
4. Urgent Field Safety Notice: ADVIA Centaur ® Systems, Dimension Vista ® Systems, and IMMULITE ® Systems. Siemens Healthcare Diagnostics Inc.; January 2016.
5. Medical Safety Alert: GOV.UK website. Estradiol immunoassays—interference from the drug fulvestrant (Faslodex®) may cause falsely elevated estradiol results. Medicines and Healthcare products Regulatory Agency, United Kingdom; March 2016.
6. Nolvadex ® FDA prescribing information: AstraZeneca Pharmaceuticals LP; January 2016.
7. ARCHITECT ® Estradiol package insert. Abbott Ireland Diagnostics Division; June 2015.