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AuraTek FDP
510(k) #K970353

510(k) SUMMARY

1.0 510(K) SUMMARY

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1.1 General Information

Date Prepared:	April 28, 1997
Device Generic Name:	AuraTek FDP
Device Trade Name:	AuraTek FDP
Applicant's Name and Address:	Organon Teknika, B.V. Veedijk 58 2300 Turnhout, Belgium
Authorized representative in the U.S.:	PerImmune, Inc. 1330 Piccard Drive Rockville, MD 20850-4396 Tel: (301) 258-5200 Contact: Fedora Daye Contreras
Establishment Registration Number:	1119752
510(k) Premarket Notification Number:	K970353

1.2 Indications for Use

AuraTek FDP is a rapid one-step gold dye particle lateral flow immunoassay indicated for the *in vitro* qualitative measurement of fibrinogen and fibrin/fibrinogen degradation products (FDP) in human urine, to be used with standard cystoscopic examination to aid in the management of patients with a history of bladder cancer.

1.3 Device Classification

AuraTek FDP is a **bladder tumor marker test system-monitoring** which has been reclassified as a **Class II** (Performance standards) device, product code 82 MMW.

1.4 Background Information

Cancer of the bladder is a disease with high prevalence among men and women in the U.S. (4th and ninth respectively among malignant diseases) and a high rate of recurrence (estimated to be 80%). Consequently, close follow-up of bladder cancer patients on a regularly scheduled basis is essential. The standard practice for follow-up of patients with a history of bladder cancer involves the use of an invasive diagnostic procedure, transurethral cystoscopy, in which the urothelium is visually inspected with a flexible or rigid endoscope.

Although there have been many attempts to develop efficient and reliable non-invasive diagnostic tests for bladder cancer, the urinary cytological examination remains the current clinical standard. However, cytology suffers from a limited sensitivity[1] (approximately 35%), particularly in low grade and low stage disease. In addition, cytology is costly, requires a specialized clinical laboratory and the results are not available to the urologist during the office visit by the bladder cancer patient.

Hemoglobin dipstick may be used as a diagnostic aid, but lacks both sensitivity and specificity for bladder tumors. In addition, a single instance of microhematuria may be attributable to a variety of causes[2]. A wide range of alternative markers and procedures have been proposed, including flow cytometry, QFIA[3], M344 antigen[4], nuclear matrix protein[5], bladder tumor associated antigen (BTA)[6], and autocrine motility factor[7]. The acceptance of alternative markers has been limited due to lack of efficacy, high expense, and test complexity. It would be useful, therefore, for the urologist to have available a rapid, point-of-care, diagnostic test that could offer high sensitivity, convenience, and rapid results to support the cystoscopic examination of bladder cancer patients.

Previously published studies have shown that elevated urinary fibrin(ogen) degradation products (FDP) are associated with the presence of bladder cancer. In particular, McCabe, et al.[8] found elevated urinary fibrinogen and FDP levels in 83% of all bladder cancer patients tested using an ELISA method. Based upon this initial study, a rapid, self-contained immunoassay device was developed (AuraTek FDP) that is similar in principle to several over the counter urinary hCG pregnancy tests. This test employs monoclonal antibodies specific for fibrinogen and fibrin(ogen) degradation products and is designed for point-of-care use in the physician's office.

1.5 Device Description

1.5.1 Description of Test Analyte

Fibrinogen is a protein found in blood plasma that is converted into fibrin in the process of blood clotting. Fibrin/fibrinogen degradation products (FDP) are protein fragments generated by the action of the fibrinolytic system (plasmin) on fibrin and fibrinogen.

1.5.2 FDPs in Bladder Cancer

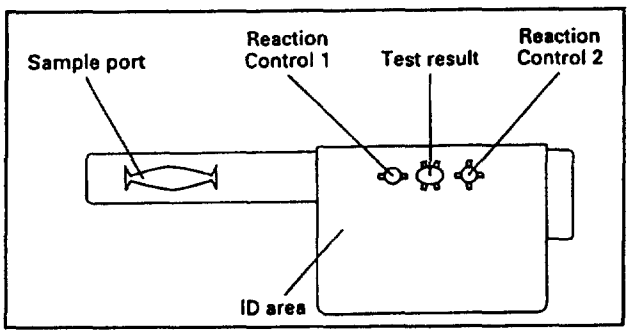
Studies have shown that increased urinary fibrin/fibrinogen degradation products (FDP) levels are associated with the presence of bladder malignancy. Wajsman et al. reported findings of significantly elevated FDP levels in patients with active bladder carcinoma[9]. Using an ELISA procedure, McCabe et al. found elevated urinary fibrinogen and FDP levels in 83% of all bladder cancer patients tested[8]. The same paper also reported a 98% specificity for patients with nonmalignant urological disease. Other studies have confirmed the utility of urinary fibrinogen and FDP measurement in patients with bladder carcinoma[10,11,12].

Tumor cells produce vascular endothelial growth factor (VEGF), which is an angiogenic factor[13]. Increased expression of VEGF has been associated with bladder tumors[14,15]. One effect of VEGF is to increase the permeability of the surrounding microvasculature. The increased permeability may lead to leakage of plasma proteins including plasminogen, fibrinogen, and various clotting factors. The clotting factors along with other factors released by the tumor cells rapidly convert the fibrinogen into an extravascular fibrin clot. This fibrin clot will act as a provisional stroma for the tumor until being replaced by mature stroma. Plasminogen may be converted to plasmin by urokinase, the plasminogen activator in the urine produced by the kidney, as well as the tumor cells. The plasmin can then break down the fibrin deposit into fibrin degradation products or FDP's.

1.5.3 Device Design

AuraTek FDP is a one-step gold dye particle immunoassay on a porous carrier. Mobile purple-red dye particles labeled with anti-FDP and fibrinogen antibody and immobile capture anti-FDP and fibrinogen antibodies are coated as discrete zones on the porous carrier. In addition a test control zone with anti-murine IgG (Reaction Control 2) is coated on the carrier. A sample placed on the device is absorbed by

the porous carrier. The rehydrated colored sol particles move through the porous carrier to the capture anti-FDP and then to the anti-murine IgG. If the sample contains FDP and/or fibrinogen, the antibody-labeled sol particles will bind in a sandwich-type reaction to the capture anti-FDP and fibrinogen antibody producing a purple-red dot in the test result window. With a negative sample, the white test result window remains unchanged at the time of reading. AuraTek FDP has the unique feature that the test run validity is double-checked with the appearance and disappearance of color in the Reaction Control 1 window and development of a purple-red dot in the Reaction Control 2 window.



1.6 Substantial Equivalence

The AuraTek® FDP in vitro diagnostic device described in this application is substantially equivalent to a currently marketed test. The BARD BTA Rapid Urine Test, manufactured by Bard Diagnostic Sciences, Bard Urological Division is designed for the qualitative measurement of an analyte associated with the presence of bladder cancer in human urine. (See Table 1.0)

Table 1.0 Substantial Equivalence of AuraTek FDP with the Bard BTA Test		
Test Name	**AuraTek FDP**	**Bard BTA**
Intended Use	**AuraTek FDP is a rapid one-step gold dye particle lateral flow immunoassay indicated for the *[in vitro* qualitative measurement] of fibrinogen and fibrin/fibrinogen degradation products (FDP) in human urine to be used with standard cystoscopic examination [to aid in the management of patients with a history of bladder cancer.]**	**The Bard BTA rapid latex agglutination test is an *[in vitro]* device intended for the [qualitative] measurement of Bladder Tumor Associated Analytes in human urine [to aid in the management of bladder cancer patients.]**
Sample Matrix	**Urine**	**Urine**
Format	**Rapid lateral flow immunoassay**	**Rapid latex agglutination test**
Analyte	**Fibrinogen and Fibrin/Fibronogen Degradation Products (FDP)**	**Bladder Tumor Associated Analytes**
Limit of Detection	**30 ng Fibrinogen Equivalents (FE) / ml**	**9.8 μg/ml Bladder Tumor Associated Analytes**
Sensitivity	**68%**	**40% (from package insert)**
Specificity	**80%**	**80% (from package insert)**

1.7 Summary of Studies

1.7.1 Analytical Sensitivity / Limits of Detection

The sensitivity of AuraTek FDP is approximately 30 ng FE/ml as defined by the amount of FDP (ng FE/ml) present in urine which consistently produces a positive test result. The unit, "ng FE/ml" refers to "fibrinogen equivalents". This represents the relative immunoreactivity of fibrin(ogen) degradation products derived from a predetermined quantity of fibrinogen in plasma.

1.7.2 Reproducibility

Qualitative reproducibility studies were conducted to determine within-day, between-day, between laboratory and between-lot variability. The within-day reproducibility study was run using a negative control sample (0 ng FE/mL), a low level control (25 ng FE/ml), and a high level control (250 ng FE/mL). All controls were tested using twenty replicates at each level. The other studies were conducted using a negative control sample (0 ng FE/mL), a low level control (65 ng FE/ml), and an intermediate level control (200 ng FE/mL). All three controls were tested in duplicate using two separate lots of devices on four separate days at four different clinical sites. All reproducibility studies demonstrated total qualitative agreement at each control level

1.7.3 High Dose Hook (Prozone) Effect

AuraTek FDP was tested using high concentration FDP specimens to assess high dose hook effects in patient samples with high concentrations of analyte. No hook effects were seen at concentrations up to 2000 ng FE/ml.

1.7.4 Interfering Substances

AuraTek FDP was performed with urine specimens containing a variety of potentially interfering substances. The tests included specimens with no detectable levels of FDP, 15 ng FE (fibrinogen equivalents)/ml and 100 ng FE/ml. Whole blood and plasma may cause positive interference with AuraTek FDP at levels greater than 0.0156% volume/volume.

Substance	Highest Concentration Tested	Highest Concentration with no Interference (1)
Hemoglobin	225 mg/dl	225 mg/dl
Albumin	10 g/l	10 g/l
Bilirubin unconjugated	206 mg/dl	206 mg/dl
Uric Acid	250 mg/dl	250 mg/dl
Disodium cromoglycate	10 mg/l	10 mg/l
Cetirizine HCl	10 mg/l	10 mg/l
Caffeine	100 mg/l	100 mg/l
Paracetamol	500 mg/l	500 mg/l
Ibuprofen	400 mg/l	400 mg/l
Acetylsalicylic Acid	500 mg/l	500 mg/l
Amoxicillin	200 mg/l	200 mg/l
Oxazepam	25 mg/l	25 mg/l
Diazepam	20 mg/l	20 mg/l
Ethanol	2000 mg/l	2000 mg/l
Desogestrel	5 mg/l	5 mg/l
Prednisone	10 mg/l	10 mg/l
Clomiphene Citrate	50 mg/l	50 mg/l
Ethinylestradiol	5 mg/l	5 mg/l
Heroin	6 mg/l	6 mg/l
Morphine	6 mg/l	6 mg/l
Tetrahydrcannabinol	6 mg/l	6 mg/l
Sodium Chloride	100 mg/l	100 mg/l
Amphetamine Sulfate	10 mg/l	10 mg/l
Chlorpromazine	50 mg/l	50 mg/l
Ascorbic Acid	30 mg/l	30 mg/l
Nicotine	20 mg/l	20 mg/l
Domperidone	20 mg/l	20 mg/l
Doxycycline	200 mg/l	200 mg/l
Methadone	6 mg/l	6 mg/l
Glucose	10 g/l	10 g/l
Red blood cells	1×10^6 / ml	1×10^6 / ml
White blood cells	5×10^4 / ml	5×10^4 / ml
Whole blood	1% vol/vol	0.0156% vol/vol (2)
Plasma	1% vol/vol	0.0156% vol/vol (2)
Serum	1% vol/vol	1% vol/vol
IgG Antibody	6.25 mg/dl	6.25 mg/dl

Notes: (1) Refers to absence of both positive and negative interference.
(2) Positive interference was found at a level of 0.125% vol/vol.

Expected Results

Clinical Sensitivity

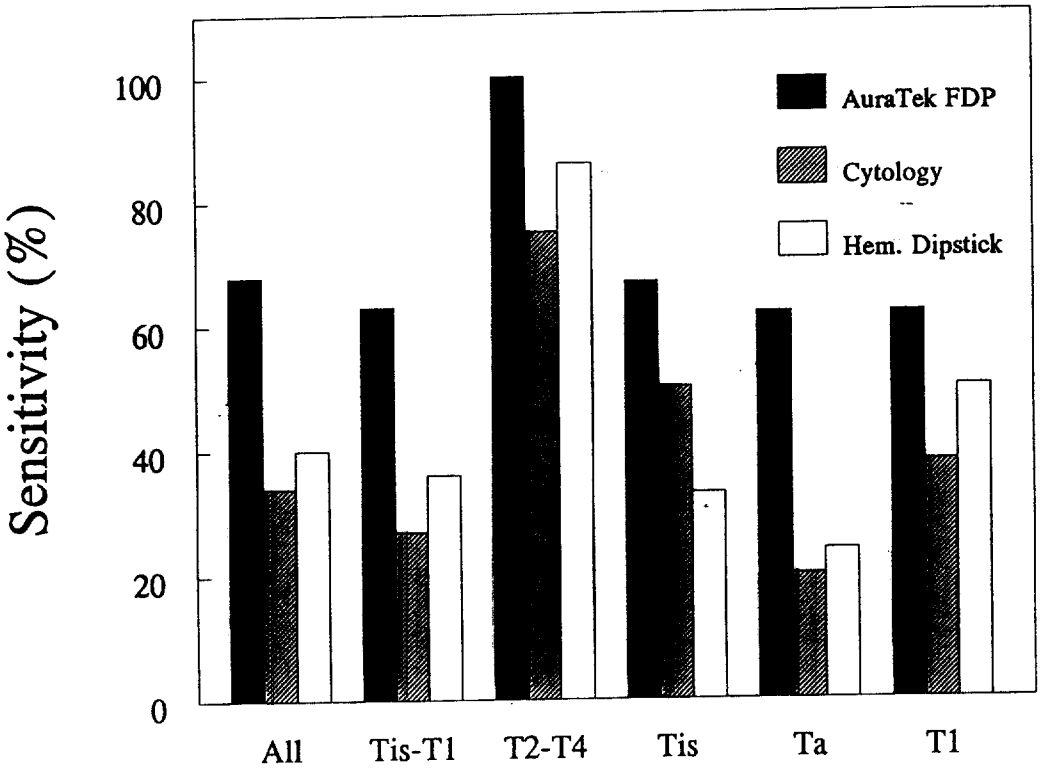
Positive urinary FDP test results may be indicative of bladder cancer in patients with a confirmed prior history of bladder cancer. A multi-center study was performed on 192 patients with a history of bladder cancer undergoing cystoscopic examination in a general urology practice. The mean age of the group was 69.1 ± 10.3 years. Seventy-three percent of the subjects were male. Subject racial distribution was 181 Caucasian subjects, 1 Asian subject, 2 African American subjects, 1 Hispanic subject, 1 Pacific Islander, 1 Indian Subconinent subject and 5 subjects of unknown racial origin. Bladder tumors were confirmed in 79 patients by positive cystoscopy results with confirmatory biopsy. The sensitivity results for the AuraTek test and urine cytology are listed in the following tables.

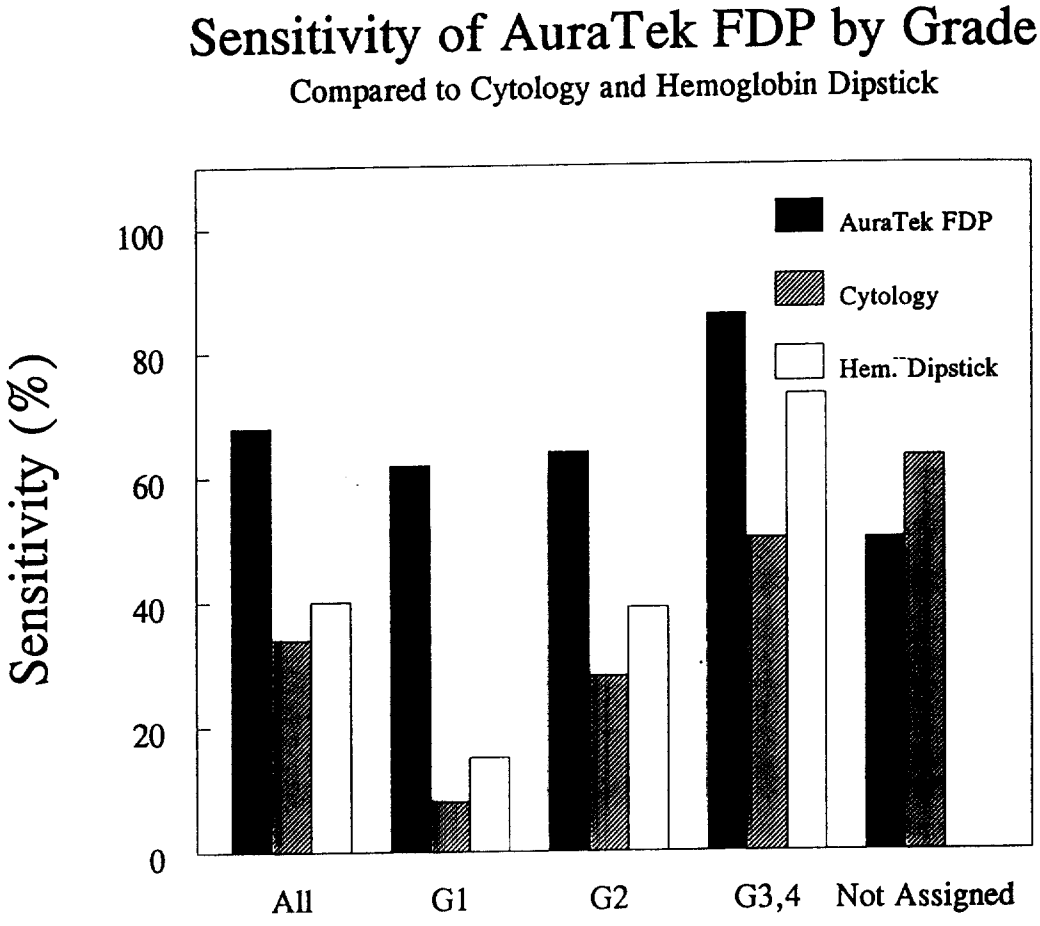
Sensitivity of AuraTek FDP by Stage

Disease Stage	Number of Subjects	AuraTek FDP Positive	AuraTek FDP 95% Confidence Interval	Cytology Positive	Cytology 95% Confidence Interval	Hemoglobin Dipstick	Hemoglobin Dipstick 95% Confidence Interval
All Stages	n=79	68% (54/79)	56.9-78.4%	34% (27/79)	23.9-45.7%	41% (32/79)	33.6-54.8%
Superficial (Tis, Ta, T1)	n=67	63% (42/67)	50.0-74.2%	27% (18/67)	16.8-39.1%	36% (28/77)	25.7-48.1%
Invasive (T2,T3,T4)	n=12	100% (12/12)	73.5-100%	75% (9/12)	42.8-94.5%	86% (12/14)	57.1-98.3%
Tis	n=6	67% (4/6)	22.3-95.7%	50% (3/6)	11.8-88.2%	33% (2/6)	4.3-77.7%
Ta	n=45	62% (28/45)	46.5-76.2%	20% (9/45)	9.6-34.6%	24% (11/45)	12.9-39.5%
T1	n=16	63% (10/16)	35.4-84.8%	38% (6/16)	15.2-64.6%	50% (8/16)	24.7-75.4%

Sensitivity of AuraTek FDP by Stage

Compared to Cytology and Hemoglobin Dipstick




Sensitivity of AuraTek FDP by Grade
Compared to Cytology and Hemoglobin Dipstick
Sensitivity (%)
100
80
60
40
20
0
AuraTek FDP
Cytology
Hem. Dipstick
All
G1
G2
G3,4
Not Assigned

Sensitivity of AuraTek FDP by Grade							
Disease Grade	Number of Subjects	AuraTek FDP Positive	AuraTek FDP 95% Confidence Interval	Cytology Positive	Cytology 95% Confidence Interval	Hemoglobin Dipstick	Hemoglobin Dipstick 95% Confidence Interval
All Grades	n=79	68% (54/79)	56.9-78.4%	34% (27/79)	23.9-45.7%	41% (32/79)	29.6-52.2%
G1	n=13	62% (8/13)	31.6-86.1%	8% (1/13)	0.2-36.0%	15% (2/13)	1.9-45.5%
G2	n=36	64% (23/36)	46.2-79.2%	28% (10/36)	14.2-45.2%	39% (14/36)	23.1-56.5%
G3, G4	n=22	86% (19/22)	65.1-97.1%	50% (11/22)	28.2-71.8%	73% (16/22)	49.8-89.3%
Not Assigned	n=8	50% (4/8)	15.7-84.3%	63% (5/8)	24.5-91.5%	0% (0/8)	0.0-36.9%

Specificity

Specificity was tested on a panel of normal, healthy subjects, on urology clinic patients being cystoscopically examined for recurrence of bladder cancer or suspicion of bladder cancer, and on general urology patients with a variety of non-bladder cancer urological disease.

Specificity of AuraTek FDP Healthy Subjects and Cystoscopy Negative Bladder Cancer Patients

Subject Type	Number of Subjects	AuraTek FDP Negative	AuraTek FDP 95% Confidence Interval
Healthy subjects	n=73	96% (70/73)	88.5-99.1%
Cystoscopy negative patients with a history of bladder cancer	n=113	80% (90/113)	72.2-87.1%

Specificity Results of AuraTek FDP on Patients with Non-Bladder Cancer Urological Disease					
Disease Category	**Disease**	**Total Evaluable Subjects**	**AuraTek FDP Negative**	**Specificity**	**95% Confidence Interval**
Total	**All Urological Disease**	**232**	**200**	**86.2**	**(81.1-90.4)**
Prostate	Benign prostatic hypertrophy	48	44	91.7	(80.0-97.7)
	Prostatitis	12	11	91.7	(61.5-99.8)
	Prostate cancer	40	34	85.0	(70.2-94.3)
	Misc. prostate	1	1	100	(2.5-100.0)
	Total Prostate Disease	101	90	89.1	(81.4-94.4)
Renal	Renal stones	12	10	83.3	(51.6-97.9)
	Renal cell carcinoma	10	9	90.0	(55.8-99.7)
	Transitional cell carcinoma	1	0	0	NA
	Misc. renal	3	1	33.3	(0.8-90.6)
	Total Renal Disease	26	20	76.9	(56.4-91.0)
Urinary Tract Infections	Urinary tract infections	13	10	76.9	(46.2-95.0)
Bladder	Interstitial cystitis	27	24	88.9	(70.8-97.7)
	Misc. bladder disease	5	3	60.0	(14.7-94.3)
	Total Bladder Disease	32	27	84.4	(67.2-94.7)
Urodynamic	Incontinence	25	23	92.0	(74.0-99.0)
	Misc. urodynamic	3	3	100	(29.2-100.0)
	Total Urodynamic Disease	28	26	92.9	(76.5-99.1)
Testes	Testicular cancer	5	5	100	(47.8-100.0)
	Misc. testicular	5	5	100	(47.8-100.0)
	TotalTesticular Disease	10	10	100	(63.1-100.0)
Miscellaneous	Misc. categories	22	17	77.3	(54.6-92.2)
Cancer*	Total Urological Cancers	56	48	85.7	(73.8-93.6)

* Includes subjects from all disease categories

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