SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Photodynamic Diagnosis System
Device Trade Name:	Karl Storz D-Light C Photodynamic Diagnosis (PDD) System
Applicant's Name and Address:	Karl Storz Endoscopy-America, Inc. 2151 E. Grand Avenue El Segundo, CA 90245
Date of Panel Recommendation:	As a component of a combination diagnostic imaging system, this device was presented and reviewed by the Oncologic Drugs Advisory Committee for the Center for Drug Evaluation and Research on December 17, 2009

Premarket Approval Application (PMA) Number: P050027

Date of FDA Notice of Approval: May 28, 2010

Expedited: not applicable

II. INDICATIONS FOR USE

The Karl Storz Photodynamic Diagnostic D-Light C (PDD) System in combination with the optical imaging drug Cysview® (hexaminolevulinate hydrochloride) for Intravesical Solution is indicated for photodynamic blue light cystoscopy, as an adjunct to white light cystoscopy for the detection of non-muscle invasive papillary cancer of the bladder in patients suspected or known to have the lesion on the basis of a prior cystoscopy.

III. CONTRAINDICATIONS:

Cysview® should not be used in the following patients:

- Patients with gross hematuria
- Patients with porphyria
- Patients with known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid
- Patients who have received BCG immunotherapy or intravesical chemotherapy within the last 90 days

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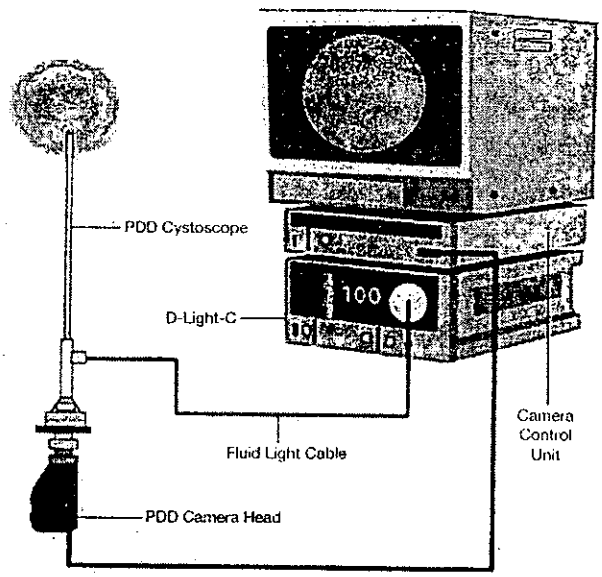
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Karl Storz D-Light C PDD System labeling.

V. DEVICE DESCRIPTION

The Karl Storz PDD System consists of the following parts: a D-light C light source, rigid PDD Telescopes, fluid light cables, the Endovision Telecam® SL / Endovision Tricam® SL PDD camera control units, and PDD camera head. The D-light C unit connects to the PDD telescope via a fluid light cable. Light from the D-light C unit is transmitted through the fluid light cable connected to the telescopes to illuminate the area to be observed. The PDD camera head is coupled to the eyepiece of the PDD telescope. The image is transmitted from the distal tip of the telescopes to the eyepiece, captured by the PDD camera head coupling, and displayed on a monitor connected to the camera system. The PDD camera head is automatically synchronized to control the light modes of the D-light C unit. A schematic figure of the essential components of the system is as follows:



The D-light C unit is a 300 watt short arc Xenon light source with two modes of operation: the white light (WL) mode and the PDD mode. The attenuated WL mode emits light in the visible spectrum ranging from 390 - 770 nm and is used for illumination of the bladder during a routine cystoscopy. The PDD mode emits light in the blue portion of the visible spectrum from 360 - 450 nm and is used to induce and view fluorescence in the bladder. Tissue fluorescence can be viewed either directly through the eyepiece of the telescopes or on a video monitor using the respective PDD camera head attached to the eyepiece of the PDD Telescopes.

The D-light C unit was used for both WL and PDD cystoscopy in the clinical studies. When the D-light C unit is turned on, it automatically defaults to the WL mode.

Refer to KARL STORZ labeling (PDD System Operators Manual: D-LIGHT-C light source; Hopkins II PDD Telescopes; Endovision TELECAM SL; Endovision TRICAM SL; and Fluid Light Cables) for information on using these devices.

Refer to the Cysview® Package Insert for information and instructions for use of the drug.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

- Currently a combination of methods are used for diagnosis of bladder cancer because no single available procedure detects all malignancies.
- Urine tests are frequently part of an evaluation, but have been nonspecific for cancer or required specialized analysis at a laboratory.
- Cystoscopy and transurethral resection or biopsies are required to histologically diagnose and stage bladder cancer for the most effective course of treatment.
- Imaging Test allows a physician to visualize organs either on a monitor or on films. These tests may include a CT scan, IVP, x-rays, MRI, and ultrasound.

VII. MARKETING HISTORY

The Karl Storz D-Light C PDD System has been marketed in Europe, Eastern Europe, the Middle East, Asia, Japan, Australia, Canada, and South America. The Karl Storz D-Light C PDD System received a CE mark in June 1998 and was first distributed in 1998. Since marketing began, 81 units have been sold to date. The PDD System has not been withdrawn from marketing for any reason relating to its safety or effectiveness

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Cystoscopy is an invasive surgical procedure carrying certain risks including the risk of urinary tract infection/sepsis, bladder perforation or other trauma to the bladder and/or urethra. Additional risks include those associated with the use of anesthesia and sedatives and the introduction of catheters, telescopes, and/or resectoscopes.

Expected risks are usually mild and temporary and may include discomfort after the procedure, temporary swelling of the urethra, a stinging sensation when passing urine for a couple days, a small amount of blood in the urine, and urine retention.

The chronic nature of renal and urinary problems and the trauma from surgery may further trigger psychological effects such as insomnia and anxiety.

Safety data collected during the Cysview® cystoscopy clinical development program were similar across studies. Data from individual studies were pooled to create integrated data sets for exposure; demographics baseline disease characteristics and concomitant medications. The clinical safety data base include a total of 1,324 patients from Studies PC B304/04 and PC B305/04 as well as patients from studies PC B201/00, B301/01,B302/01, and B303/01, all presented in NDA 22-555. An overview of Adverse Events (AE) experienced in the integrated studies is presented below.

Adverse Events in Controlled Studies

	Cysview® & Cystoscopy* N=1,324	
MedDRA Preferred Term	**All Grades**	**Severe**
Patients with at least one treatment -related AE	161 (12.2%)	16 (1.2%)
Bladder spasm	32 (2.2%)	4 (0.3%)
Dysuria	24 (1.8%)	0 (0%)
Hematuria	23 (1.7%)	1 (0.1%)
Bladder pain	23 (1.7%)	3 (0.2%)
Procedural pain	18 (1.4%)	0 (0%)
Urinary retention	17 (1.3%)	2 (0.2%)
Headache	14 (1.1%)	0 (0%)

*Incidence of Adverse Reactions in ≥ 1% of Patients in Clinical Studies (Safety Population)

- The adverse reactions were typically reported during or after cystoscopy.
- Eleven (11) serious adverse reactions occurred; single cases of tachycardia, chest pain, pyrexia (two instances in the same patient), bladder spasm, hematuria, and lung disorder, as well as two cases each of sepsis and urinary retention.
- Twelve (12) patients receiving Cysview® had at least one adverse event leading to study discontinuation. Two (2) of these events were considered related to Cysview®; tachycardia and chest pain in the same patient. Two events leading to study discontinuation resulted in death; neither was considered related to Cysview®.
- There were no important differences or trends in the incidence, frequency, or severity of adverse events based on gender or age.

See Cysview® labeling for a complete list of Adverse Events.

IX. SUMMARY OF PRECLINICAL STUDIES

A. BENCH TESTING:

Each of the components of the PDD system was tested and reviewed to verify the non-clinical design specifications and performance requirements. All results of these tests were within specifications and are acceptable.

a. Fluorescence Spectroscopy Systems in General:

KSEA provided literature describing testing of general fluorescence spectroscopy systems that assessed the safety of "blue" light exposure to tissue for various prototype systems. The wavelengths of the excitation systems centered at 337 nm, 380 nm, and 460 nm for testing. Cytotoxicity from these systems was lower or comparable to those from white light (xenon) systems currently in use for colposcope and other diagnostic procedures.[1, 2, 3]

b. Excitation and Emission Filters:

The PDD system employs three sets of optical filters to assist in fluorescence detection. The filters in the D-Light include an attenuation filter and a low pass filter. In the white light (WL) mode, the attenuation filter within the D-light reduces output from the 300-watt xenon bulb to 1/10 of its original value. This attenuation filter permits the user to observe the tissue under "normal" camera-CCU settings of shutter speed and gain. In the blue light (ALA) mode, a low pass filter allows full flux from 370-425 nm for maximum 5-aminolevulinic acid excitation. The low-pass filter is supplemented by a blocking filter to cut off stray light above 600 nm. The combination of ALA (low pass and blocking) filters allows maximum excitation of the 5-aminolevulinic molecule from the blue light while shielding stray red light from the user. A blue filter within the scope aids in observing the green fluorescence by further filtering out the background blue light. The purpose of this testing was to validate the optical characteristics of three sets of optical filters required to assist in fluorescence detection.

Test Results of Optical Characteristics of Filters

Within the D-Light	Wave Lengths	% of Total
90% attenuation	Blocks all	10%
Low pass	370 – 425 nm	>95 %
Blocking Side 1	535 – 635 nm	<1%
Blocking Side	640 – 740 nm	<1%
Eyepiece	380 – 430 nm 450 – 800 nm	<1% >96 %

c. **PDD D-Light Light Source:**

The spectral irradiance or flux density of the integrated excitation wave-bands were measured. The purpose of testing was to compare the energy emitted from the WL and the PDD/ALA modes of the D-Light Source. Testing results are indicated as an average of three measurements.

Distance from tissue (cm)	Area illuminated cm^2	Irradiance of white light (mW/cm^2)	Irradiance of blue light (mW/cm^2)
1	2.06	52	32
3	18.54	5.8	3.5
5	2.1	2.1	1.3
10	206	0.52	0.32

System	Output WL (mW)	Output ALA (mW)	Output WL (lm)	Output ALA (lm)
D-Light w/cable	298	203	79	2.9**
D-Light w/cable/scope	107	65	28	0.94**

** Instrument calibrated for white light. Accuracy in the violet-blue region is uncertain, but the photopic response curve is near minimum in this wavelength band

d. **Endovision Telecam SL Camera System and Endovision Tricam SL PDD Camera System**:

The Endovision Telecam® SL Camera Control Unit, Endovision Tricam® SL PDD Camera Control Unit, PDD camera heads, and Fluid Light Cables (collectively referred to as the camera system) are cleared through Pre-Market Notification (510K) process. No significant modifications were required for integration into the PDD system.

e. **PDD Telescopes:**

Testing was performed on all four models of the PDD telescopes to validate optical performance.

Model	Direction of view(degrees)	Depth of Field (mm)	Magnification, Max	Resolution Max (Lp/mm)	Distortion, Max
27005AIA	0	4-100	8	25	-11%
27005BIA	25	4-100	8	25	-11%
27005CIA	60	3-100	8	25	-21%
27005FIA	12	6-75	6	14	N/A

Testing was performed to validate the resolution, light, and temperature output of the PDD system using a D-light unit, Fluid light cable Telecam CCU and Urocam PDD Beamsplitter camera.

Resolution

Test	Results
Resolution at 5 / 10 / 25 mm	20.2 lp/mm /11.0 lp/mm / 5.0 lp/mm
Maximum output in WL mode	24.4 lumens
Minimum output in WL mode	0.93 lumens
Bandwidth in WL mode	350-685 nm
Max. output in ALA mode	0.75 lumens
Min. output in ALA mode	0.028 lumens
Bandwidth in ALA mode	350-440nm
Optical intensity in WL mode	Unchanged after 2 hours
Optical intensity in ALA mode	Unchanged after 2 hours

Light Output

Output in WL/ALA mode	In air	In water
Cable output WL/ALA	251.6 / 165.9 mW	251.6 / 165.9 mW
Cable output WL/ALA	67.6 / 2.36 lumen	.67.6 / 2.36 lumen
Scope output WL/ALA	93.4 / 53.9 mW	93.4 / 53.9 mW
Scope output WL/ALA	24.4 / 0.75 lumen	24.4 / 0.75 lumen

Temperature

Location	Maximum Temperature in air WL/ALA (°C)	Maximum Temperature in saline, WL/ALA(°C)
Distal tip	27.8 / 29.9	21.2 / 21.2
Logo block	24.9 / 27.7	18.4 / 19.4
Light post	25.4 / 28.8	18.7 / 19.9
Ocular	24.4 / 26.5	18.6 / 19.6

The temperature of the scope did not change over a period of two hours.

f. Electrical Safety:

The D-light C light source and the Telecam/Tricam SL PDD Camera System were tested and determined to be in compliance with IEC 60601-1, 2nd Edition, 2nd Amendment. System level testing was previously performed on the Karl Storz Autofluorescence (AF) system (P020008) and was accepted as applicable to the PDD system. EMC testing was conducted on the PDD telescope (27005BIA) with a resectoscope and ValleyLabs Force FX at maximum settings. The PDD system has passed electrical safety and EMC testing.

B. <u>STERILIZATION:</u>

Telecam®Tricam® Camera heads and PDD telescope

Test	Purpose	Acceptance Criteria	Pass/fail
AAMI TIR30:2003	Validation of cleaning	3 Log reduction	Pass
ANSI/AAMI ST58:2005 Over Kill method	Validation of High level disinfection	SAL 10^{-6}	Pass
AAMI TIR 12:2004 Over Kill method	Validation of EtO Sterilization	SAL 10^{-6} Residuals: EtO, EO <20mg/device	Pass
AAMI TIR 12:2004 Over Kill method	Validation of Steam Sterilization	SAL 10^{-6}	Pass

X. SUMMARY OF CLINICAL INVESTIGATIONS

The results of the clinical investigation are included in NDA 22-555 for Cysview®. Please refer to the Cysview® drug labeling for study results.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental clinical information is included in NDA 22-555 for Cysview®. Refer to Cysview® drug labeling for study results.

XII. PANEL MEETING RECOMMENDATION

The Oncologic Drugs Advisory Committee reviewed this application on December 17, 2009 as a component of a combination diagnostic imaging system and recommended approval. See Summary of Panel meeting on the CDER website located at: http://www.fda.gov/ohrms/dockets/ac/acmenu.htm

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINCAL STUDIES

A. SAFETY CONCLUSIONS

Preclinical bench testing indicated that the PDD System conformed to the product specifications and validated the system design. Clinical safety of the PDD System combined with use of the PhotoCure's drug Cysview® was assessed by a review of adverse events. Based on the results of the studies, the safety profile of Cysview® cystoscopy indicates that this diagnostic agent indicated for photodynamic cystoscopy is safe, well tolerated and poses little risk in patients with known or suspected bladder cancer. There was no indication that administered Cysview® contributed to the frequency or severity of AEs, other than what could be expected for WL cystoscopy and TURB procedures

B. EFFECTIVENESS CONCLUSIONS:

The Integrated Analysis of Efficacy in NDA 22-555 is focused on the data from the pivotal Study PC B305/04 and the supportive Study PC B304/04. Using the prespecified analytical criteria, Study 305 achieved success upon one of the study's co-primary endpoints. Specifically, the proportion of Cysview® group patients who had a Ta or T1 lesion detected only with blue

light (16%) exceeded the prespecified 10% threshold ($P < 0.01$). However, the desired statistical success was not achieved for the study's second co-primary endpoint. This endpoint was a "superiority" comparison of the follow-up "recurrence rate" between the Cysview® group and the white light group. The results showed a "recurrence" rate of 47% in the Cysview® group and 56% in the white light group ($P = 0.03$).

C. OVERALL CONCLUSIONS:

Based on the preclinical and clinical testing, FDA concludes that there is reasonable assurance that the use of Cysview® with the PDD System in blue light (PDD/ALA) mode is safe and effective as a diagnostic method for the detection of non-muscle invasive papillary cancer of the bladder as an adjunct to white light cystoscopy

XIV. CDRH DECISION:

CDRH issued an approval order on May 28, 2010.

The device manufacturing facilities were inspected and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS:

Information on the use of the PDD System can be found in the PDD Operator Manual. Instructions for use for using the PDD system with Cysview® can be found in the package insert for Cysview®. Post-approval requirements and restrictions can be found in the respective device and drug approval orders.

XVI. REFERENCES

1. Brookner ,Carrie K. et.al., Safety analysis: Relative Risks of Ultraviolet Exposure from Fluorescence Spectroscopy and Colposcopy are Comparable. Photochemistry and Photobiology. (1997) 65(6) 1020-1025.

2. Kriska, Tamas. Et. Al., Effect of 5-ALA on tissue culture Hyperresistance to Photosensitized Lipid Peroxidation and Apoptotic Killing in 5-Aminolevulinate-treated Tumor Cells Overexpressing Mitochondrial GPX4. Free Radical
Biology and Medicine, (1994) 33 (10) pp. 1389-1402.

3. Andley, Usha P. et. al., Action Spectrum for Cytotoxicity in the UVA- and UVB- Wavelength Region in Cultured Lens Epilethial Cells. Investigative Opthalmology and Visual Science, (1994) 35 (2) pp. 367-373.