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NCCN Guidelines Panel: Bladder Cancer

On behalf of Photocure, I respectfully request the NCCN Bladder Cancer Committee review the enclosed clinical data on Blue Light Cystoscopy™ with Cysview® for inclusion in the Bladder Cancer clinical practice algorithms.

Specific Changes: Include Blue Light Cystoscopy with Cysview at the time of surveillance and TURBT recommendations within the following algorithmic steps: Initial Evaluation and Primary Evaluation/ Surgical Treatment Steps within BL-1, Secondary Surgical Treatment Steps within BL-2, Cystoscopy Steps within BL-E Table 1, and Evaluation Step within BL-3.

FDA Clearance: BLC with Cysview is approved by the FDA for use in the cystoscopic detection of carcinoma of the bladder, including CIS, among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy, or in patients undergoing surveillance cystoscopy for carcinoma of the bladder. BLC with Cysview is approved for repeat use and following intravesical therapy.

Rationale: The 2016 updates to both the American Urological Association (AUA) and the European Association Urology Guidelines recommend that in a patient with NMIBC, a clinician SHOULD offer BLC with Cysview at the time of TURBT, if available, with the AUA specifying its use to increase detection and decrease recurrence; sixteen publications demonstrate the added benefit of BLC with Cysview for a more complete TURBT; use at surveillance offers improved follow-up assessment; prior BCG therapy and prior resections do not significantly alter detection rate; and new evidence demonstrates the benefit of changed patient management in 14% of patients due to more accurate diagnosis in post-market, “real-world” patient registry data derived from a population of mixed BLC user experience levels.

We submit the following articles in support of the proposed change. Data of particular interest, published recently, have been highlighted as **** Of Major Importance * Of Importance**

1. **Smith A, Daneshmand S, Patel S, et al. Patient-reported outcomes of blue light flexible cystoscopy with hexaminolevulinate (HAL) in the surveillance of bladder cancer: results from a prospective multi-center study. *BJU Int.* 2018 Jul 6. doi: 10.1111/bju.14481. [Epub ahead of print]
2. ** Daneshmand S, Bazargani ST, Bivalacqua TJ, et al. Blue light cystoscopy for the diagnosis of bladder cancer: Results from the US prospective multicenter registry. *Urol Oncol.* Published Online Ahead of Print: May 30, 2018.
3. **Daneshmand S, Patel S, Lotan Y, et al. Efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. *J Urol.* 2018 May;199(5):1158-1165.
4. *Jacqmin D, Jichlinski P, Molinier L, et al. Observational studies requested by European health authorities: governmental interference or an enhancement of everyday urological practice? The Hexvix observational patients evaluation study as an example of what to expect. *Urol. Int.* 2017; 99:358-366

5. Gakis G, Fahmy O. Systematic review and meta-analysis on the impact of hexaminolevulinate versus white-light guided transurethral bladder tumor resection of progression in non-muscle Invasive Bladder Cancer. *Bladder Cancer*. 2016 Jul 27;2(3):293-300.
6. Mariappan P, Rai B, El-Mokade I, et al. Real-life experience: early recurrence with Hexvix photodynamic diagnosis-assisted transurethral resection of bladder tumour vs good-quality white light TURBT in new non-muscle-invasive bladder cancer. *Urology*. 2015 Aug; 86(2):327-31.
7. **Gallagher KM, Gray K, Anderson CH, et al. 'Real-life experience': recurrence rate at 3 years with Hexvix photodynamic diagnosis-assisted TURBT compared with good quality white light TURBT in new NMIBC-a prospective controlled study. *World J Urol*. 2017 Dec;35(12):1871-1877.
8. Lykke MR, Nielsen TK, Ebbensgaard NA, et al. Reducing recurrence in non-muscle-invasive bladder cancer using photodynamic diagnosis and immediate post-transurethral resection of the bladder chemoprophylaxis. *Scand J Urol*. 2015 Jun;49(3):230-6.
9. Gakis G, Ngamsri T, Rausch S, et al. Fluorescence-guided bladder tumour resection: impact on survival after radical cystectomy. *World J Urol*. 2015 Oct;33(10):1429-37.
10. Witjes JA, Gomella LG, Stenzl A, et al. Safety of hexaminolevulinate for blue light cystoscopy in bladder cancer. a combined analysis of the trials used for registration and postmarketing data. *Urology*. 2014 Jul;84(1):122-6.
11. *Lane GI, Downs TM, Soubra A, et al. Tolerability of repeat use of blue light cystoscopy with hexaminolevulinate for patients with urothelial cell carcinoma. *J Urol*. 2017 Mar;197(3 Pt 1):596-601.
12. *Apfelbeck M, Grimm T, Kretschmer A, et al. Follow-up of high-risk bladder cancer - Is it safe to perform fluorescence endoscopy multiple times in the same patient? *Urol Oncol*. 2017 Oct;35(10):602.e19-602.e23.
13. Kamat AM, Cookson M, Witjes JA, et al. The impact of blue light cystoscopy with hexaminolevulinate (HAL) on progression of bladder cancer: a new analysis. *bladder cancer*. 2016 Apr 27;2(2):273-278.
14. Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol*. 2013;64(5):846-54.
15. Grossman HB, Stenzl A, Fradet Y, et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. *J Urol* 2012; 188: 58-62.
16. Herman GG, Mogensen K, Carlsson S et al. Fluorescence-guided transurethral resection of bladder tumours reduces bladder tumour recurrence due to less residual tumour tissue in Ta/T1 patients: a randomized two-centre study. *BJU Int*. 2011 Oct;108(8 Pt 2):E297-303.
17. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urol*. 2010;184(5):1907-13.