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ADIS DRUG Q&A

Hexaminolevulinate: a profile of its use with blue-light cystoscopy in the diagnosis of bladder cancer

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Abstract Hexaminolevulinate [Cysview® (USA); Hexvix® (EU)], an ester derivative of 5-aminolevulinate, is a valuable option for the diagnosis of bladder cancer when used in conjunction with blue-light (BL) cystoscopy. In clinical trials, the addition of hexaminolevulinate-guided BL cystoscopy to white-light (WL) cystoscopy was generally better at detecting non-muscle-invasive bladder cancer lesions than WL cystoscopy alone, as assessed by a number of endpoints (e.g. increased number and rate of lesion detection), leading to increased rates of complete treatment decisions. Add-on hexaminolevulinate-guided BL cystoscopy reduced tumour recurrence rates relative to WL cystoscopy alone in follow-up studies and, although further studies are needed, may potentially improve survival-related outcomes. Hexaminolevulinate is generally very well tolerated when used to guide BL cystoscopy, with the most common adverse events (i.e. haematuria, dysuria, pain and bladder spasm) being expected as a consequence of the resection procedure.

Adis evaluation of hexaminolevulinate–guided blue light cystoscopy as an add-on to white-light cystoscopy in the diagnosis of bladder cancer
Has high sensitivity and specificity rates
↑ detection of NMIBC lesions relative to WL cystoscopy alone, leading to more complete treatment decisions
↓ rates of tumour recurrence and may potentially improve some survival-related outcomes
Very well tolerated with the same most common adverse events as WL cystoscopy alone
Estimated to be cost saving relative to WL cystoscopy alone, as its addition ↑ quality-adjusted life-years and, due to better lesion detection, ↓ future treatment costs
BL blue light, *NMIBC* non-muscle-invasive bladder cancer WL white light, ↑ increases, ↓ decreases

Why add blue-light cystoscopy to white-light cystoscopy when diagnosing bladder cancer?

Bladder cancer often requires ongoing monitoring, surveillance and/or treatment to reduce recurrence and prevent progression, as non-muscle-invasive bladder cancer (NMIBC) lesions have a tendency to recur [1–5]. Correct diagnosis and removal of all visible lesions using cystoscopy and transurethral resection of bladder tumour (TURBT) are crucial in the diagnosis and treatment of bladder cancer. Management of each patient will vary, depending on the biopsy findings (i.e. histology, grade, depth of invasion) and the estimated likelihood of recurrence and progression. NMIBC lesions include [1, 2]:

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- *Flat carcinoma* in situ *(Cis or Tis)* High malignancy potential; generally progressive; require timely and intensive treatment. Lesions may be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied.
- *Noninvasive papillary carcinomas largely confined to the mucosa (Ta)* Low-grade lesions have a high risk of recurrence but a low risk of progression; require risk-specific treatment and continued surveillance. High-grade lesions are generally progressive and require intensive treatment in a timely manner.
- *Noninvasive papillary carcinomas largely confined to the submucosa or lamina propria (T1)* High malignancy potential; generally progressive; require timely and intensive treatment.

Incomplete identification of lesions leads to incomplete initial TURBT, persistent tumours and early recurrence of NMIBC [1–5]. White light (WL) cystoscopy detects large, protruding lesions (e.g. T1 lesions), but may not detect flat (e.g. Cis) or smaller lesions. When added to WL cystoscopy, hexaminolevulinate-guided blue-light (BL) cystoscopy increases the detection of NMIBC lesions (particularly smaller lesions and Cis) relative to WL cystoscopy alone, and is included in EU [1] and US [2] guidelines for the diagnosis and treatment of NMIBC.

This article provides a narrative review of the use of hexaminolevulinate-guided BL cystoscopy in the diagnosis of bladder cancer.

Why use hexaminolevulinate to guide BL cystoscopy?

BL cystoscopy uses the photoactive nature of certain compounds, such as 5-aminolevulinic acid (5-ALA) and its derivatives, to enhance the visual differentiation between normal and neoplastic tissue [4–7]. These compounds accumulate preferentially in neoplastic tissue and are metabolized to form photoactive porphyrins that fluoresce red when illuminated with BL (wavelength 375–440 nm), thereby providing better visualization of tissue that is suspicious for tumours than the use of WL alone [4–7].

The first agent used in the BL detection of NMIBC lesions was 5-ALA, an endogenous and non-fluorescent compound involved in the biosynthesis pathway of haeme (Fig. 1a) [8]. Exogenous administration of 5-ALA overwhelms the haeme pathway, producing an excess protoporphyrin IX, a fluorescent haeme precursor that preferentially accumulates in tumour cells and is detectable by BL cystoscopy (Fig. 1b) [8]. However, the use of 5-ALA, which is not approved for photodynamic detection, is limited by some of its pharmacological properties [3–5].

Hexaminolevulinate [Hexvix® (EU) [9]; Cysview® (USA) [10]] was developed to have a better pharmacological profile than 5-ALA [4]. It is an ester derivative of 5-ALA, and consists of a lipophilic hexyl moiety bound to 5-ALA [11]. Relative to 5-ALA, hexaminolevulinate has several advantages in BL diagnosis of NMIBC lesions, including increased protoporphyrin IX fluorescence at lower concentrations (e.g. a 2-fold increase in fluorescence at a 45-fold lower concentration [12]), a shorter instillation time (1 vs 4 h) [13, 14], faster and greater penetration of the urothelium tissue in vitro [12], and higher specificity for malignant urothelial carcinoma [14].

What is the approved indication for hexaminolevulinate?

Hexaminolevulinate-guided BL cystoscopy is indicated in the diagnosis of bladder cancer as an adjunct to WL cystoscopy in patients with a known or high suspicion of bladder cancer [9, 10]. It is not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer [10], and must be performed by healthcare professionals who are trained and proficient in its use. Table 1 provides a summary of the use of hexaminolevulinate in the diagnosis of bladder cancer in the EU [9] and USA [10].

Based on the evidence available at the time of regulatory assessment, hexaminolevulinate-guided BL cystoscopy does not appear to represent a risk when used as follow-up in patients with bladder cancer (European Medicines Agency) [9] or is not indicated for repetitive use (US FDA) [10]. Studies in the clinical-practice setting in 62–80 patients with multiple (2–12) instillations of hexaminolevulinate found no significant differences between the first and subsequent use of hexaminolevulinate-guided BL cystoscopy with regard to its tolerability and safety profiles, with no induction of allergization against the substance being shown [15, 16]. The results of a clinical study evaluating the repeated use of hexaminolevulinate-guided BL flexible cystoscopy in the surveillance office setting [17] are awaited with interest.

What was the diagnostic effectiveness of hexaminolevulinate-guided BL cystoscopy?

The use of hexaminolevulinate-guided BL cystoscopy as an add-on to WL cystoscopy in the diagnosis of bladder cancer has been evaluated in many clinical studies; the

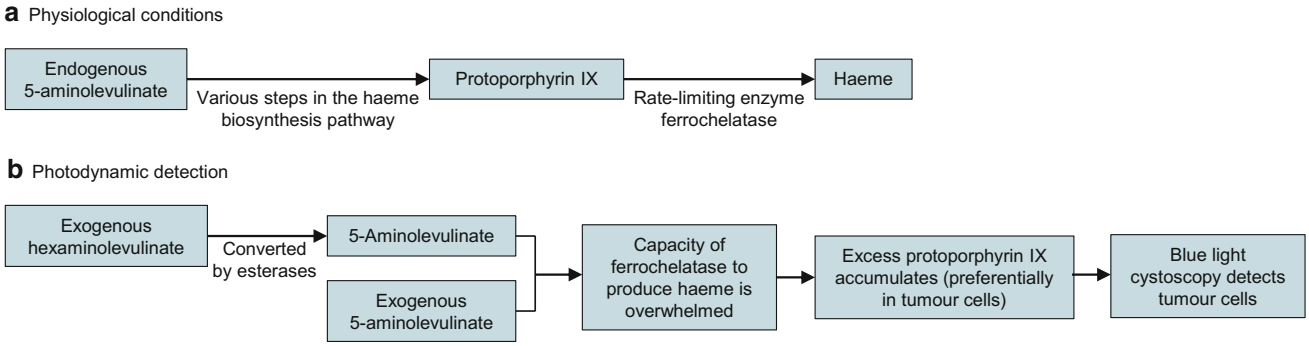

Fig. 1 Overview of (**a**) the haeme biosynthesis pathway under physiological circumstances, and (**b**) its disruption by the addition of exogenous hexaminolevulinate or 5-aminolevulinate for the purpose of photodynamic detection with fluorescence cystoscopy [8]

discussion in this section focuses on data from clinical trials [18–30], pooled analyses of data from trials of similar design [31], well-conducted meta-analyses of clinical trial data [32–36], studies in the clinical-practice setting [37–52] and studies of BL flexible cystoscopy [17, 53–58]. Three phase 3 trials (B301, B302 and B303; n = 146–211) [18–21] and a clinical practice study from the Blue Light Urologic Endoscopy group (the BLUE study; n = 305) [37] primarily assessed tumour detection, whereas other randomized trials and their follow-up periods primarily assessed tumour recurrence (n = 86–402) [22–30].

Sensitivity and specificity

At the lesion level, hexaminolevulinate-guided BL cystoscopy as an add-on to WL cystoscopy was associated with numerically higher sensitivity rates in the detection of NMIBC lesions than WL cystoscopy alone (92 vs 68% sensitivity in the phase 3 B302 trial [19, 20] and 93.8 vs 78.2% sensitivity in the BLUE study [37]).

At the patient level in B302 [19], no statistically significant between-group differences (BGDs) in sensitivity (87 vs 83%) or specificity (82 vs 72%) were reported. Across several clinical trials [18–21, 23, 27, 37], the rate of false-positives was 11–39% with add-on hexaminolevulinate-guided BL cystoscopy and 10–31% with WL cystoscopy alone. However, in another trial in which all patients received TURBT with WL cystoscopy (including those that subsequently received hexaminolevulinate-guided BL cystoscopy) [25], the corresponding rates were 32 and 55%. In the BLUE study [37], the rate of false-negatives was 2.2% with add-on hexaminolevulinate-guided BL cystoscopy and 25.8% with WL cystoscopy alone. The addition of hexaminolevulinate-guided BL cystoscopy also improved sensitivity and/or specificity rates relative to WL cystoscopy alone in clinical-practice studies in 53–90 patients with NMIBC [38–44].

Tumour detection

Hexaminolevulinate-guided BL cystoscopy was a better detection method for NMIBC than WL cystoscopy alone [18–23, 27, 37], in terms of numerically higher detection rates and additional detected lesions (at both the lesion and patient level) in the studies in which tumour detection was the primary outcome [18–21, 37], as well as in tumour recurrence trials that also assessed tumour detection [22, 23, 27].

The findings in individual trials are supported by tumour detection rates in a pooled analysis [31] of the three B301-3 trials [18–21], as well as meta-analyses of 9 [32] or 16 [33] trials.

- *All lesion types* Add-on hexaminolevulinate-guided BL cystoscopy was associated with a higher overall detection rate than WL cystoscopy alone, with a significant 19.0% (95% CI 15.2–23.6) BGD in the proportion of lesions detected. One or more additional tumours were detected in 15% (95% CI 9.8–21.1) of patients [33].
- *Cis lesions* Detection rate was higher with add-on hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy alone in all analyses. One or more Cis lesions were detected in 87 versus 75% of 174 patients (p = 0.006) [31]; odds ratio (OR) 12.37 (95% CI 6.34–24.13; $p < 0.001$) [32]. Of all patients with Cis lesions, 26.7% had one or more additional Cis lesions detected only by hexaminolevulinate-guided BL cystoscopy [32]; significant BGD in the proportion of Cis lesions detected (15.7%; 95% CI 6.9–24.5) [33].
- *Ta lesions* Detection rate was higher with add-on hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy alone (OR 4.898; 95% CI 1.937–12.390; $p < 0.001$) [32]. Of all patients with Ta or T1 lesions, 24.9% ($p < 0.001$) had at least one additional Ta or T1 lesion detected only by

Table 1 Prescribing summary of hexaminolevulinate in conjunction with blue-light cystoscopy in the diagnosis of bladder cancer in adults in the EU [9] and USA [10]. Consult local prescribing information for further details

What is the approved indication of hexaminolevulinate (Hexvix®) and contraindications to its use in the EU?	
Indication	In conjunction with BL cystoscopy as an adjunct to WL cystoscopy to contribute to the diagnosis and management of bladder cancer in patients with a known or high suspicion of bladder cancer
Contraindications	Porphyria; hypersensitivity to hexaminolevulinate or any of the excipients of the solvent
What is the approved indication of hexaminolevulinate (Cysview®) and contraindications to its use in the USA?	
Indication	In the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy
	Use with the Karl Storz D-Light C Photodynamic Diagnostic system to perform cystoscopy with the BL setting (Mode 2) as an adjunct to the WL setting (Mode 1)
Contraindications	Porphyria; gross haematuria, BCG immunotherapy or intravesical chemotherapy within the past 90 days; known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives
How is hexaminolevulinate available?	
Vial of powder containing 100 mg of hexaminolevulinate HCl (equivalent to 85 mg of hexaminolevulinate) + a vial (EU; USA) or prefilled syringe (EU) of solvent for intravesical solution; special storage conditions are not required prior to reconstitution	
How should hexaminolevulinate powder be reconstituted?	
Reconstitute with 50 mL of solvent under aseptic conditions	
Reconstituted solution contains hexaminolevulinate HCL 2 mg/mL (equivalent to hexaminolevulinate 1.7 mg/mL; 8 mmol/L)	
Use reconstituted solution immediately; if not used immediately, refrigerate for up to 2 h at 2–8 °C	
How should hexaminolevulinate be instilled and diagnostic testing performed?	
Drain bladder before instillation of reconstituted solution	
Insert 50 mL of the reconstituted solution into the bladder via a catheter; patient should retain the solution for ≈60 min	
After the bladder is evacuated, start the BL examination within ≈60 min (do not perform if >3 h after instillation)	
If the bladder retention time is considerably <1 h, start the BL examination ≥60 min after instillation	
Examine and map the entire bladder using WL cystoscopy first followed by BL cystoscopy before initiating any surgical procedures	
Normally, take biopsies of all mapped lesions under WL and verify complete resection by switching to BL	
What warnings/precautions pertain to the use of hexaminolevulinate-based BL cystoscopy?	
Hypersensitivity	Serious anaphylactic/anaphylactoid reactions may occur; ensure advanced life support facilities (EU) or trained personnel and therapies (USA) are readily available
Failed detection	All malignant lesion may not be detected; always perform WL cystoscopy followed by BL cystoscopy
False fluorescence	May occur due to inflammation, cystoscopic trauma, scar tissue or previous bladder biopsy
Patients at high-risk of bladder inflammation	EU: exclude widespread bladder inflammation by cystoscopy before administration (may lead to ↑ porphyrin build-up and ↑ risk of local toxicity upon illumination, and false fluorescence); avoid BL cystoscopy if widespread inflammation is noted with WL cystoscopy
How should hexaminolevulinate be used in special patient populations?	
Children	Safety and efficacy have not be established in patients aged <18 years
Pregnant women	As a precautionary measure, avoid use (EU); use only if the potential benefits outweigh the potential risks to the fetus (USA) [data are limited]
Nursing mothers	Discontinue breast-feeding during use (EU) or use with caution (USA) [not known whether hexaminolevulinate is excreted in human milk]

BL blue light, *HCl* hydrochloride, *WL* white light, ↑ increased

hexaminolevulinate-guided BL cystoscopy [32]; significant BGD in proportion of Ta lesions detected (5.9%; 95% CI 1.4–10.3) [33].

- *T1 lesions* Based on limited data, differences between add-on hexaminolevulinate-guided BL cystoscopy and WL cystoscopy alone were not significant in either meta-analysis (OR 2.25; 95% CI 0.999–5.081 [32]; BGD in proportion −1.2%; 95% CI −3.3 to −5.7) [33].

The addition of hexaminolevulinate-guided BL cystoscopy to WL cystoscopy also improved the detection of bladder cancer lesions, especially Cis lesions, relative to WL cystoscopy alone in studies of patients with NMIBC in the clinical-practice setting (n = 48–403 patients) [38–47]. For example, in a clinical-practice study in 403 patients [44], add-on hexaminolevulinate-guided BL cystoscopy detected 6.8% more cancer lesions and 25% more Cis lesions ($p < 0.0001$) than WL cystoscopy alone, as well as

detecting ≥1 additional positive lesions in 10% of patients and providing a diagnosis of NMIBC in 2.2% of patients that would otherwise be missed. In this analysis, hexaminolevulinate-guided BL cystoscopy would need to be added to WL cystoscopy in 16 patients to detect one additional patient with a cancerous lesion [44].

Tumour detection with BL flexible cystoscopy

The use of hexaminolevulinate-guided BL flexible cystoscopy in the outpatient or office-based setting is increasing, as improved tumour detection rates may potentially lead to less extensive and more cost effective management of patients with bladder cancer [17]. In a phase 3 study conducted in the clinical office setting in 17 US academic institutions, 234 patients under surveillance because of their high risk of tumour recurrence were randomized to WL flexible cystoscopy alone or in combination with hexaminolevulinate-guided BL flexible cystoscopy [17]. According to preliminary results, almost half (44%) of patients were referred to the operating room within 6 weeks because of suspected tumour recurrence, where WL and hexaminolevulinate-guided BL cystoscopy were repeated [17].

In smaller (n = 20–73) studies, hexaminolevulinate-guided BL flexible cystoscopy was reliable in detecting bladder tumours, with detection rates that were equivalent [53] or almost equivalent [54, 55] to those with hexaminolevulinate-guided BL rigid cystoscopy [54, 55], and/or comparable to standard rigid WL cystoscopy [54] and better than those with standard flexible WL cystoscopy [55–58].

Complete treatment plans

As a result of better lesion detection, more complete NMIBC treatment plans could be made following tumour detection with add-on hexaminolevulinate-guided BL cystoscopy than after WL cystoscopy alone, as reported in the following trials:

- *B302 trial* [19] 14% of patients had their proposed WL cystoscopy-based treatment plan changed after hexaminolevulinate-guided BL cystoscopy, and 81.3% had their proposed treatment plan confirmed. Hexaminolevulinate-guided BL cystoscopy was useful as an add-on and for selecting further management options in 66 and 51% of cases, respectively.
- *B303 trial* [21] 17% of patients received a more complete treatment plan based on add-on hexaminolevulinate-guided BL cystoscopy than based on WL cystoscopy alone. Hexaminolevulinate-guided BL cystoscopy was useful as an add-on and for making further treatment decisions in 78 and 42% of cases, respectively.
- *Tumour recurrence trial* [27] Add-on hexaminolevulinate-guided BL cystoscopy had significantly ($p \leq 0.001$) higher rates of changes in tumour grading and treatment decisions than WL cystoscopy alone (e.g. a decision of no treatment was changed to treatment with bacillus Calmette-Guérin in 7.7 vs 1.4% of cases, no treatment changed to mitomycin-C in 4.2 vs 0.7%, and overall changes in risk grading with a change in treatment plan in 19.0 vs 6.3%).

Tumour recurrence, disease progression and survival

Regardless of the length of follow-up, the overall tumour recurrence rate (primary endpoint) was significantly lower in patients with NMIBC who had received add-on hexaminolevulinate-guided BL cystoscopy than in those who received WL cystoscopy alone in most follow-up studies [22–24, 26–28], with the exception of some relatively small studies [25, 29, 30] (Table 2).

The addition of hexaminolevulinate-guided BL cystoscopy to WL cystoscopy also showed significant benefits over WL cystoscopy alone with regard to a number of other NMIBC tumour recurrence-related endpoints in several trials (Table 2) [22–30]. Moreover, although the trials were not adequately powered for subgroup analysis, findings in various subgroups generally suggest a lower recurrence rate with add-on hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy alone (Table 2) [22–24, 26, 28].

Meta-analyses also indicate that the risk of NMIBC tumour recurrence with add-on hexaminolevulinate-guided BL cystoscopy is lower than that with WL cystoscopy [34–36]. In a network analysis of 15 trials, the risk of NMIBC tumour recurrence with hexaminolevulinate-guided BL cystoscopy was lower than with WL cystoscopy (OR 0.58; 95% CI 0.45–0.74; $p < 0.0001$) and did not differ significantly from narrow-band imaging (OR 1.11; 95% CI 0.55–2.101) [34]. Likewise, in the subgroup of 9 hexaminolevulinate trials in a meta-analysis of 14 5-ALA/hexaminolevulinate trials, relative to WL cystoscopy alone, the addition of hexaminolevulinate-guided BL cystoscopy significantly reduced the relative risk (RR) of bladder cancer at recurrence at 3–12 months (RR 0.76; 95% CI 0.62–0.93) and >1 year (RR 0.75; 95% CI 0.62–0.92), and the risk of disease progression (RR 0.51; 95% CI 0.28–0.96), but did not reduce the risk of mortality or recurrence at <3 months to a significant extent [36].

A meta-analysis of five studies found that the rate of progression of bladder cancer was significantly lower with

Table 2 Tumour recurrence in clinical trials of add-on hexaminolevulinate-guided blue-light cystoscopy vs white-light cystoscopy alone in patients with non-muscle invasive bladder cancer (the primary outcome in all trials was recurrence rate)

Results (hexaminolevulinate-guided BL cystoscopy vs WL cystoscopy)
6-week follow-up [22] (*n* = 72 vs 64)
Overall 6-week recurrence rate (% of pts): 11.1*** vs 31.2
6-week recurrence rate by tumour type (% of pts): Cis 4.3** vs 27.8; TaG3 10 vs 22.2; T1G1–3 15.4** vs 35.1; high-grade: 17.2* vs 37
9 –month [23] **and long-term (median 4.5 years) follow-up** [24] (9-month ITT *n* =271 vs 280; PP *n* = 200 vs 202)
Overall 9-month recurrence rate (% of pts): 47* vs 56 (ITT); 36* vs 46 (PP)
Time for 50% of pts to reach recurrence: ≈330 vs ≈270 days [23]
Progression to muscle-invasive BC: 5 vs 7 pts [23]
Recurrence rate by tumour type: significant* decrease in pts with recurrent BC or TaG1/2; no BGD in pts with primary BC [23]
Median time to recurrence: 16.4* vs 9.4 months [24]
1–year follow-up [25] (*n* = 59 vs 74)
Recurrence rate (% of pts): 16.9 vs 31.1 at 4 months; 16.3 vs 23.5 at 1 year; overall 30.5 vs 47.3
Time for 25% of pts to reach recurrence: ≈280* vs ≈170 days (50% of pts in both groups had not reached recurrence by day 400)
1.5 year follow-up [26] (*n* = 41 vs 45)
Recurrence rate (% of pts): 2.4*** vs 13.3 at 3 months; 17.1* vs 40 at 1.5 years
Recurrence-free survival (% of pts; co-primary endpoint): 91*** vs 56.3 at 1 year; 82.5*** vs 50.6 at 1.5 years
Recurrence-free survival in subgroups with multi-focal lesions or primary, recurrent, 'non-aggressive'or 'aggressive' tumours: significant* decrease with hexaminolevulinate-guided BL cystoscopy (no BGD in pt subgroup with a single lesion)
Median time to first recurrence: 13.6*** vs 7.0 months
Recurrence of lesions with a worse grade than the initial histology: 0 vs 5 pts
2-year follow-up [30] (*n* = 54 vs 50)
Recurrence rate (% of pts): 8.7 vs 11.4 at 9 months; 2.4 vs 3.2 at 1 year; 12.2 vs 23.3 at 2 years; 37.5 vs 45.9 overall
2-year follow-up [27] (initial *n* = 125 vs 114) **and up to 4 years of follow-up** [28]
Recurrence rate (% of pts): 7.2** vs 15.8 at 3 months; 21.6** vs 32.5 at 1 year; 31.2*** vs 45.6 at 2 years; 35.6† vs 51.9 at 3 years; 40.8 † vs 58.8 at 4 years
Recurrence rate by BC characteristics at 2 years (% of pts): multiple lesions 35.4* vs 54.0; single lesions 23.3 vs 35.3; primary BC 24.3* vs 37.1; recurrent BC 41.2* vs 59.1
Progression rate (% of pts): 2.4 vs 4.4 at 1 year; 4 vs 7 at 2 years
3-year follow-up [29] (*n* = 86 vs 82)
Overall recurrence rate: 20 vs 17% of pts at 3 months; 16 vs 22% at 1 year; 10.6 vs 15.2% at 3 years
Progression rate (% of pts): 3.1 vs 4.5 at 3 years

BC bladder cancer, *BGD* between-group difference, *Cis* carcinoma in situ, *BL* blue light, *ITT* intent-to-treat population, *PP* per protocol population, *pt(s)* patient(s), *T1* submucosal papilloma or carcinoma, *Ta* mucosal papilloma or carcinoma, *WL* white light

* $p \leq 0.05$, ** $p < 0.01$, *** $p \leq 0.001$, † significant BGD (p value not reported)

hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy (6.8 vs 10.7% of patients; median OR 1.64; 95% CI 1.10–2.4; $p = 0.01$) [35]. Of note, disease progression results depend on the definition of disease progression in NMIBC. When data from the retrospective study with a median follow-up time of 4.5 years [24] (Table 2) were re-analyzed using a new proposed definition, additional patients in both the hexaminolevulinate-guided BL cystoscopy and WL cystoscopy alone groups progressed (12.2 vs 17.6%) and the time to progression was significantly ($p = 0.05$) longer with hexaminolevulinate-guided BL cystoscopy [59].

In the clinical-practice setting (n = 190-808), the addition of hexaminolevulinate-guided BL cystoscopy was also effective in reducing tumour recurrence [48–50] and improving survival-related outcomes (i.e. overall [49, 51], cancer-specific [51], recurrence-free [49, 51] and/or progression-free [52] survival). For example, in the study in 808 patients with bladder cancer who underwent complete TURBT, rates of early recurrence (i.e. at the first follow-up cystoscopy) were significantly lower with hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy (13.6 vs 30.9% of patients; OR 2.9; 95% CI 1.6–5.0; $p < 0.001$) [48], as were rates of 3-year recurrence (42.2 vs 48.8%) and overall and risk-group adjusted recurrence-free survival ($p \leq 0.01$) [49].

In a retrospective single-centre study in 224 patients who underwent subsequent radical cystectomy for bladder

cancer after fluorescence-guided TURBT [51], Kaplan-Meier estimates of recurrence-free survival (77.8 vs 52.4% of patients), cancer-specific survival (83.9 vs 59.7%) and overall survival (74.0 vs 56.5%) at 3 years were significantly ($p < 0.05$) higher with hexaminolevulinate-guided BL cystoscopy than with WL cystoscopy. Moreover, hexaminolevulinate-guided BL cystoscopy was an independent predictor of improved survival after radical cystectomy [51]. In contrast, in a multicentre study in 549 patients with bladder cancer, the use of hexaminolevulinate-guided BL cystoscopy during primary or final TURBT did not independently affect 3-year rates of cancer-specific (32%) or overall mortality (40%) after radical cystectomy to a statistically significant extent [60].

What is the tolerability profile of hexaminolevulinate?

Hexaminolevulinate is associated with minimal systemic absorption following bladder instillation for ≈1 [61] or 2 h [62], and is very well tolerated. The absolute bioavailability of radiolabelled hexaminolevulinate was 7% in healthy volunteers [61], and the systemic absorption of hexaminolevulinate 4, 8, or 16 mmol/L was ≈5% in patients with bladder cancer [62]; no skin sensitivity or adverse reactions could be attributed to its use [62].

The addition of hexaminolevulinate-guided BL cystoscopy to WL cystoscopy in the diagnosis of bladder cancer was very well tolerated in clinical trials and the post-marketing setting. The tolerability profile and frequency of adverse events reported in the post-marketing period (>400,000 hexaminolevulinate-guided procedures to date) is comparable to that in pivotal trials despite the broader inclusion criteria for its use in the real-world setting.

A pooled safety analysis of hexaminolevulinate-guided BL cystoscopy [63] included data from six registration trials [18–21, 23, 25, 64], in a total of 1324 and 499 hexaminolevulinate-guided BL cystoscopy and WL cystoscopy recipients, respectively (safety set), and 9 years of post-marketing data in >200,000 patients. In the pooled registration trials, 44–58% of patients receiving hexaminolevulinate-guided BL cystoscopy reported at least one treatment-emergent adverse event (TEAE), with almost all (97%) of TEAEs being mild to moderate in severity and not related to hexaminolevulinate. Overall, it appears that the addition of hexaminolevulinate-guided BL cystoscopy for bladder tumour resection adds very little risk to that seen with WL cystoscopy alone (41% of recipients of WL cystoscopy alone reported an adverse event) [63]. In pooled trials that directly compared add-on hexaminolevulinate-guided BL cystoscopy and WL cystoscopy alone (n = 533 and 499), the most common TEAEs were renal and urinary disorders (25.7 and 23.4% of patients), gastrointestinal disorders (6.8 and 6.8%), urinary tract infection (5.3 and 5.0%), and procedural pain (5.3 and 4.0%) [63]. According to the EU summary of product characteristics, the most common TEAEs across clinical studies in hexaminolevulinate-guided BL cystoscopy recipients involved urinary tract-related disorders, including bladder spasm (2.4% of patients), dysuria (1.8%), bladder pain (1.7%) and haematuria (1.7%) [9]. Of the 183 unique serious TEAEs reported in the pooled analysis, none were considered to be probably related to hexaminolevulinate-guided BL cystoscopy and eight events in six patients had an uncertain relationship [63]. Less than 1% of patients discontinued hexaminolevulinate-guided BL cystoscopy because of a TEAE [63].

During ≈9 years of post-marketing in European countries and the USA, hypersensitivity reactions possibly related to hexaminolevulinate-guided BL cystoscopy were reported in four patients (two cases each of anaphylactoid reactions and possible hypersensitivity) [63]. Repeated use of hexaminolevulinate-guided BL cystoscopy has not been associated with anaphylaxis-related TEAEs [15, 16, 63]. Nevertheless, as there is a potential risk of serious anaphylactic/anaphylactoid reactions to hexaminolevulinate instillation, trained personnel and advanced life support facilities should be readily available (Table 1).

None of the rare and generally mild changes in laboratory or physical examination findings or vital signs in the pooled analysis were considered to be related to hexaminolevulinate-guided BL cystoscopy [63].

Is hexaminolevulinate-guided BL cystoscopy cost effective?

The addition of hexaminolevulinate-guided BL cystoscopy to WL cystoscopy appears to be cost saving. In modelled analyses of the cost utility of hexaminolevulinate-guided BL cystoscopy versus WL cystoscopy in the detection of bladder cancer from a national healthcare payer perspective, hexaminolevulinate-guided BL cystoscopy was estimated to be cost-saving relative to WL cystoscopy in the USA [65], Italy [66] and England/Wales [67], as hexaminolevulinate-guided BL cystoscopy reduced recurrence rates and the requirement for repeated treatment procedures, and improved utility [e.g.quality-adjusted life years (QALYs) gained] and effectiveness scores, regardless of the time horizon used (lifetime [66, 67] or 5 years [65]).

In a modelled cost-consequence analysis in Canada, the addition of hexaminolevulinate-guided BL cystoscopy to WL cystoscopy increased healthcare payer costs over the 5-year period, but decreases in disease recurrence and/or

progression over the longer-term may reduce the need for hospital care in the future, potentially leading to cost effectiveness and even cost savings [68].

Moreover, in a prospective study from a UK healthcare payer perspective, office-based WL flexible cystoscopy and/or hexaminolevulinate-guided BL flexible cystoscopy was cost saving relative to inpatient WL cystoscopy, as office-based treatment was less costly and provided more QALYs [58].

What conclusions can be made regarding hexaminolevulinate–guided tumour diagnosis?

Hexaminolevulinate-guided BL cystoscopy is a valuable addition to WL cystoscopy in the diagnosis of NMIBC in patients who are suitable candidates for its use. According to current EU guidelines on the diagnosis of NMIBC [1], fluorescence-guided (e.g. hexaminolevulinate-guided) biopsies should be performed when the equipment is available, as WL cystoscopy alone may not identify all lesions and hexaminolevulinate-guided BL cystoscopy is more sensitive than conventional procedures for the detection of malignant tumours (particularly Cis). The US guidelines [2] state that, when available, BL cystoscopy should be offered to the patient at the time of TURBT to increase detection and decrease recurrence of tumours, and should be considered in patients with a history of NMIBC with normal cystoscopy and positive cytology. The use of add-on hexaminolevulinate-guided BL cystoscopy in the detection of NMIBC is based on the following clinical evidence.

- *Selectivity and sensitivity* Associated with high sensitivity and specificity rates.
- *Tumour detection* Detects more lesions, especially with regard to high-risk Cis lesions, than WL cystoscopy, leading to an increased proportion of patients with a complete treatment plan. Office-based BL flexible cystoscopy provides reliable tumour detection and is increasing in popularity.
- *Impact on long-term outcomes* Reduces tumour recurrence relative to WL cystoscopy and, based on limited data, may improve some survival-related outcomes (further studies are needed).
- *Tolerability* Very well tolerated, with only a few reports of hypersensitivity reactions including anaphylactic/anaphylactoid reactions.
- *Pharmacoeconomic considerations* BL rigid and flexible cystoscopy is predicted to be cost saving relative to WL cystoscopy due to improvements in clinical outcomes and utility and decreases longer-term costs.

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Compliance with ethical standards

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