Hal-guided transurethral resection of bladder tumours in adult patients with suspected non-muscle invasive bladder cancer.

Fact check and comments on the Evaluation Report

Section	Statement in the report	Correction
Section 3: Background	The report describes 5-ALA only as an orally administered agent.	In some countries this was administered intra-vesically.
Organisational implications	*"…special equipment must be used for HAL-guided TUR-BT, **some of which must be replaced regularly** to maintain the high quality of the procedures. NBI-guided TUR-BT does not have these challenges some of which must be replaced regularly to maintain the high quality of the procedures."*	See note below on equipment
Sections 7.1.2 & 8.1.2	*The expert committee misses a description of the informant's experience with HAL-guided TUR-BT, as it could in principle be someone who has not worked with the technology for long.*	The clinician interviewed is an experienced urologist with many years of significant experience in the use of HAL-guided TUR-BT in Denmark, prior to the replacement of BLC-enabled equipment with NBI-enabled equipment. [redacted]
Section 7.2.2	*"The Scientific Committee also notes that the applicant advises against the use of HAL in a patient group that is particularly relevant according to Danish and European guidelines, namely patients with inflammatory conditions in the bladder, where the differential diagnosis may be CIS. The expert committee notes that inflammatory bladder conditions are very common in the relevant NMIBC population, due to age, comorbidities, effects of the cancer disease or its treatment (e.g. BCG). Exclusion of patients with inflammatory bladder conditions would thus exclude a large part of the relevant population, but the committee notes that this is not consistent with clinical practice."*	The use of the product in patients with high risk bladder inflammation, such as after BCG treatment, pertains ONLY to a t**emporary time span** immediately after instillation. It is considered standard care *not* to perform cystoscopy immediately after instillation to allow the last instillation to take effect. Furthermore, this also applies to white light cystoscopy and Narrow Band Imaging immediately after instillation due to the inflammation in the bladder and the challenges to identify tumors. The applicant recommends using BLC again 6 weeks after the last instillation, which is the same timeframe as for WLC or NBI (4-6 weeks in clinical practice, also using BLC).

Section 8: Expected lifespan of hardware	*"The applicant describes a lifetime of the light cables of +2 years, but this information has not been validated by the manufacturer….."* *"The Technical Committee therefore considers that the applicant's estimated lifetime of +2 years is extremely unrealistic. The technical committee estimates that the cables for HAL-guided TUR-BT last between 6 months and 1 year, which is shorter than the cables used for NBI and white light."* *"Next, the technical committee…. ….points out that HAL-guided TUR-BT requires a more powerful blue light bulb, which will eventually burn out and the effect will deteriorate."*	This information has been gathered from clinicians globally and equipment manufacturers over the course of the last 15+ years. Cables used today for BLC are fibre cables, which was not the case when BLC was in general use in Denmark (these were fluid cables). BLC fibre cables have an equal lifespan to those used for WLC. With respect to the lamp, this statement was true for the older generation Xenon lamps however these are no longer used. The lamps now are LED lamps which have approximately 30,000 hours of use in terms of lifespan.
Section 9.4	*The Scientific Committee also emphasizes that the estimates of progression risk used are considered overestimated as the applicant has used progression rates corresponding to a high-risk population.*	The underlying risk of progression was based on a blending of the high, intermediate, and low risk K-M curves in Vedder et al, so to this extent we are modelling the overall population. The four studies that Maisch used for progression estimates were unselected patient groups and therefore the HR reflects the overall risk modification.
Section 6 & Summary	Overall assessment of level of evidence	Although there are inevitable methodological limitations for any non-blinded diagnostics study which are reflected in the study GRADEs, the fact remains that there are multiple mutually consistent studies supporting the benefit of BLC in terms of the 12-month recurrence free outcome, which was the DTC primary outcome of interest. By contrast, the evidence for the benefit of NBI (the primary DTC comparator) for the same outcome is slight to absent. We would urge the committee to consider the report in the light of the critical PICOs defined in the decision problem.