NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Synergo for non-muscle-invasive bladder cancer

1 Technology

1.1 Description of the technology

Synergo uses radiofrequency-induced thermo-chemotherapeutic effect (RITE) to improve how chemotherapy is given to treat non-muscle-invasive bladder cancer. It delivers controlled radiofrequency radiation (non-ionising microwave radiation), which heats the superficial layers of the bladder wall, and simultaneously flushes the bladder with a chemotherapy drug (thermo-chemotherapy). The drug solution is continuously pumped out of the bladder, cooled, and recirculated to prevent overheating. A miniature antenna in the catheter emits radiofrequency radiation directed at the bladder wall tissue, at a depth which does not generate heat on the external surface of the bladder avoiding injuries to surrounding organs.

Synergo is an intravesical irrigation system combined with an energy-delivering unit. The system has a radiofrequency generator that delivers radiofrequency energy at 915 MHz (the lower limit of microwave electromagnetism). It also includes a drug circulating unit and a microprocessor with application-specific software. The user interface consists of a computer, monitor with touch screen, and barcode reader. The software monitors and records treatment parameters in real time during the treatment session. People receiving Synergo therapy are typically treated as an outpatient. There is no need for general anaesthesia during treatment. Local anaesthesia may be used to insert the treatment catheter. Synergo is most

likely to be administered by healthcare professionals such as bladder cancer nurse specialists in secondary and tertiary care.

1.2 Relevant diseases and conditions

Synergo is intended for use in people with intermediate-risk non-muscle-invasive bladder cancer or people with high-risk cancer whose disease has not responded to intravesical BCG therapy, or in whom intravesical BCG therapy is not available, intolerable or cannot be delivered safely.

Most bladder cancers (75 to 80 percent) are non-muscle-invasive, meaning the cancerous cells are contained within the most superficial layer of the bladder wall (uroepithelium) and do not involve the underlying muscle layer. Non-muscle-invasive bladder cancer is classified as stage Ta when the tumour is confined to the uroepithelium. It is classified as stage T1 when there is spread into the connective tissue layer between the urothelium and the muscle wall. It is also graded on the characteristics of the tumour from G1 (or papillary urothelial neoplasm of low malignant potential [PUNLMP]; least aggressive and slow growing) to G3 (or high grade papillary urothelial carcinoma; most aggressive and fast growing). Carcinoma in situ is a non-papillary (flat) form of tumour consisting of early, high-grade cancer cells confined to the superficial layer of the bladder wall.

It is estimated that around 20,500 people are diagnosed with bladder cancer in the UK each year; around 9,400 of whom have invasive bladder cancer at diagnosis and 11,100 of whom have carcinoma in situ, other bladder cancer, or bladder cancer of uncertain or known behaviour (2016 to 2018; My Diagnosis Counts, Fight Bladder Cancer). According to Cancer Research UK's bladder cancer statistics, in 2017 bladder cancer was the eleventh most common cancer in the UK and the 9th most common cause of cancer death in the UK, accounting for 5,612 deaths (3% of all cancer deaths) in that year (Cancer Research UK bladder cancer statistics are for invasive cancer only [ICD-10 code C67]). For people with stage 1 bladder cancer (cancers that have grown into the connective tissue layer of the bladder wall but have not reached the muscle layer), around 80% of people survived their cancer for 5

years or more (Cancer Research UK, 2018). In some people, non-muscle-invasive bladder cancer may come back after treatment (known as recurrence). According to a recent trial on the use of BCG in people with high-risk non-muscle-invasive bladder cancer (NIMBUS trial; Grimm et al. 2020), approximately 15% of these people experienced tumour recurrence within 2 years following intravesical BCG therapy.

Bladder cancer is three times more common in men than women (My Diagnosis Counts, Fight Bladder Cancer). Although bladder cancer is more common in men, women are more likely to present with advanced stage cancer and typically have a less favourable prognosis and outcomes once diagnosed. The condition is more common in older adults, with most new cases diagnosed in people aged 60 and above. It is also more common in White people than in Asian or Black people. Other factors known to increase the risk of developing bladder cancer include smoking, exposure to certain industrial chemicals, long-term or repeated urinary tract infections (UTIs), having had bladder cancer before and a family history of bladder cancer.

1.3 Current management

People with suspected bladder cancer are usually offered a transurethral resection of bladder tumour (TURBT). This involves the complete removal of all visible papillary tumours, where feasible, and obtaining a sample for biopsy. The outcome of TURBT is used to risk stratify cancers and they are regarded as either low, intermediate, or high risk depending on the size and number of tumours and the histological stage and grade of the cancer. People with high-risk non-muscle-invasive bladder cancer should be offered another TURBT no later than 6 weeks after the first resection. This early re-resection is used to try to ensure complete cancer clearance and improve staging. Treatment for people with a confirmed diagnosis of non-muscle-invasive bladder cancer is guided by this risk classification. In patients with low-risk non-muscle-invasive bladder cancer, TURBT alone may be sufficient. In patients with intermediate or high-risk cancers, additional treatment is usually offered.

Intravesical chemotherapy (usually mitomycin C) is given to people with intermediate-risk non-muscle-invasive bladder cancer. Some centres may offer intravesical device-assisted chemotherapy such as hyperthermic chemotherapy (using heat and chemotherapy) or electromotive drug administration (electrically stimulated chemotherapy). These emerging treatments are aimed at improving the delivery and efficacy of chemotherapy.

A choice of intravesical BCG or radical cystectomy (surgery to remove the whole bladder) is offered to people with high-risk non-muscle-invasive bladder cancer. People in whom symptoms have not responded to intravesical chemotherapy may be considered for intravesical BCG therapy and people for whom symptoms have not responded to intravesical BCG therapy may be considered for cystectomy. The choice of treatment should be based on a discussion with the person being treated, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy. The discussion should take into consideration the type, stage and grade of cancer and the risk of disease progression, as well as the benefits and risks of both treatments.

NICE's guideline on bladder cancer: diagnosis and management is relevant to this care pathway.

The guidelines for the management of bladder cancer by West Midlands expert advisory group for urological cancer recommends that when induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy (surgery to remove the whole bladder) or further intravesical therapy with hyperthermic mitomycin C, if radical cystectomy is unsuitable, declined by the patient, or if the bladder cancer that recurs is intermediate- or low-risk.

NICE interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer recommends that RITE therapy should only be used with special arrangements for clinical governance, consent, and audit or research.

1.4 Regulatory status

Synergo received a CE mark in 2001 (last updated in May 2019) as a Class IIb medical device.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Reduced rates of tumour recurrence
- Reduced disease progression
- Reduced need for cystectomy in some people, resulting in reduced morbidity and mortality associated with cystectomy
- No requirement for general anaesthesia
- Additional treatment option for people in whom BCG is indicated but cannot be administered due to contraindications or patient preference

The benefits to the healthcare system claimed by the company are:

- Reduced number of cystectomies performed, potentially leading to fewer post-surgery complications
- Reduced hospital stay
- Treatment moved from an inpatient to outpatient setting
- Reallocation of hospital resources
- Additional treatment option for people in whom BCG is indicated when supply of the drug is limited or delayed

2 Decision problem

Population	People with intermediate or high-risk non-muscle-invasive bladder cancer (as determined by NICE guideline NG2).
Intervention	Radiofrequency-induced thermo-chemotherapy effect (RITE) therapy using the Synergo SB-TS 101 System
Comparator(s)	Intermediate and high-risk: •Other device-assisted chemotherapy options (hyperthermic or electromotive drug administration) Intermediate-risk: •Passive intravesical chemotherapy

	High-risk: •Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy •Cystectomy
Outcomes	The outcome measures to consider include: •Recurrence rates and time to recurrence •Disease progression and changes to treatment indicative of advanced disease •Rates of cystectomy •Complete response rate in papillary non-muscle-invasive bladder cancer •Complete response rate for carcinoma in situ •Disease-specific and overall survival •Health-related quality of life •Treatment tolerability • Length of hospital stay •Treatment delivery rates in inpatient or outpatient settings •Rates of failed treatment delivery due to device-related issues •Adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which can include scenarios in which different numbers and combinations of devices are needed when relevant.
Subgroups to be considered	Where evidence allows the following subgroups may be considered: •People in whom previous intravesical therapy has failed •People with papillary tumours only •People with carcinoma in situ, with or without papillary tumour (ablative therapy) •Subgroups based on risk group (intermediate or high), stage and grade of cancer •Intravesical agent used
Special considerations, including those related to equality	Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Women diagnosed with bladder cancer are more likely to present at an advanced stage and have worse prognosis and outcomes than men. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to have a disability under the Equality Act.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	Yes*
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	*Synergo is contraindicated in pregnancy. Pregnancy is a protected characteristic under the Equality Act 2010.	
Any other special considerations	Special consideration is needed when treating people with metallic or magnetic implants (such as pacemakers and prostheses). For people with implantable cardiac devices, it is advised to obtain approval and follow-up from a cardiologist before treatment with Synergo. Awareness to excessive sensitivity is needed in cases of metallic prostheses in the pelvic region.	

3 Related NICE guidance

Published

- Bladder cancer: diagnosis and management (2015) NICE guideline NG2
- Suspected cancer: recognition and referral (2015, last updated 2017) NICE guideline NG12
- Transurethral laser ablation for recurrent non-muscle-invasive bladder cancer (2019) NICE interventional procedures guidance 656
- Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer (2019) NICE interventional procedures guidance 638
- Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer (2018) NICE interventional procedures guidance 628
- Laparoscopic cystectomy (2009) NICE interventional procedures guidance 287
- Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy (2008) NICE interventional procedures guidance 258

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association of Cancer Physicians
- Bladder and Bowel Foundation
- British Association of Urological Nurses
- British Association of Urological Surgeons (BAUS)
- British Society of Interventional Radiology
- British Uro-Oncology Group
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Radiologists
- Royal College of Surgeons
- The Association for Cancer Surgery (BASO ~ The Association for Cancer Surgery)
- UK Oncology Nursing Society
- Urology Foundation

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Action Bladder Cancer UK
- Bladder & Bowel UK
- Fight bladder cancer
- Macmillan cancer support
- Tenovus cancer care