NICE National Institute for Health and Care Excellence

NICE guidance

Synergo for non-muscle-invasive bladder cancer

HealthTech guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces MIB226 and MTG61.

1 Recommendations

1.1 Synergo shows promise for high-risk non-muscle-invasive bladder cancer that has not responded to or has recurred after Bacillus Calmette-Guerin (BCG) treatment, or when people cannot or do not want to have BCG treatment. However there is not enough good-quality evidence to support the case for routine adoption. Synergo should only be used with special arrangements as outlined by NICE interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer.

1.2 Research is recommended on the benefits and costs of Synergo for high-risk non-muscle-invasive bladder cancer. This is to address the uncertainty in the evidence base and to inform a revised cost analysis to assess the impact of Synergo on cystectomy rates or repeat cystoscopies in people who cannot have a cystectomy. Because randomised controlled trials are challenging in this patient population, further collection and analysis of observational and NHS audit data is recommended. Find out details of required research outcomes in the section on further research in this guidance.

Why the committee made these recommendations

Synergo delivers chemotherapy and microwave energy to the bladder. Clinical experts advise that chemotherapy using Synergo would be used in the NHS for high-risk non-muscle-invasive bladder cancer after BCG has not worked, or if someone cannot or does not want to have BCG.

Synergo offers an alternative treatment to the limited options available for these people, which include radical cystectomy (removal of the bladder) or regular cystoscopies (a procedure to look inside the bladder to check for tumours and remove them if necessary). The experts advise that using Synergo for intermediate-risk cancer is unlikely to be practical. Also, there are other effective treatments available for these people.

There is some evidence that chemotherapy using Synergo could reduce the chance of the

cancer returning. But this observation comes from a trial that does not reflect how Synergo is likely to be used in the NHS.

Cost modelling for Synergo is uncertain and does not reflect how it is likely to be used in the NHS. Because of this and the limitations in the clinical evidence, further research is recommended into using Synergo in high-risk non-muscle-invasive bladder cancer.

2 The technology

Technology

2.1 Synergo treats non-muscle-invasive bladder cancer (NMIBC) using a radiofrequency-induced thermo-chemotherapeutic effect (RITE). It heats the superficial layers of the bladder wall using controlled radiofrequency radiation (non-ionising microwave radiation), and flushes the bladder with a chemotherapy drug at the same time. The drug solution is continuously pumped out of the bladder, cooled, and recirculated to prevent overheating. A miniature antenna in the catheter directs radiofrequency radiation at the bladder wall tissue. Synergo aims to improve the delivery and efficacy of chemotherapy with the objective of reducing tumour recurrence and disease progression. It is another treatment option for NMIBC, in addition to Bacillus Calmette-Guerin (BCG) therapy and radical cystectomy.

2.2 The technology 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. Synergo is CE marked as a class IIb medical device.

Care pathway

2.3 NICE has not made recommendations on the position of device-assisted chemotherapy treatments like Synergo in the NHS clinical pathway for bladder cancer.

2.4 Expert advice suggests the technology is being used in the NHS as an alternative to further intravesical treatment or cystectomy in high-risk NMIBC if:

- it has not responded to BCG treatment or has recurred after treatment, or
- when people cannot or do not want to have BCG treatment, or when it's not available.

Innovative aspects

2.5 The innovative aspects are the use of radiofrequency radiation (non-ionising microwave radiation) to deliver controlled electromagnetic energy directly to the walls of the bladder, along with instillations of the bladder with chemotherapy. This microwave-induced hyperthermia is designed to make the chemotherapy more effective.

Intended use

2.6 Synergo is intended for intermediate-risk or high-risk NMIBC. People have Synergo as outpatients in specialist centres. There is no need for general anaesthesia during treatment, but local anaesthetic lubricating gel may be used to insert the treatment catheter. Synergo is administered by healthcare professionals such as bladder cancer nurse specialists or consultant urologists trained in using Synergo, in secondary and tertiary care settings.

Costs

2.7 The total annual cost of Synergo therapy is £11,650 per patient (based on 12 treatment sessions). This includes the following costs:

- administering mitomycin C (MMC): £4,585 per patient
- the annual lease for the Synergo device: £327 per patient
- consumables: £490 per use
- 70 minutes of Band 7 Nurse time to administer the treatment with Synergo:

£72.

For more information about the technology, see the website for Synergo.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence submitted by the company. This section summarises that review. Full details of all the evidence are in the project documents on the NICE website.

Clinical evidence

The main clinical evidence comprises 19 studies

3.1 The evidence assessed by the EAC included 19 studies reported across 20 full text publications. Of the included studies, 5 were comparative (3 randomised controlled trials [RCTs] and 2 observational studies) and 14 were single-arm observational studies. The comparative evidence included a total of 595 people with intermediate-risk or high-risk non-muscle-invasive bladder cancer (NMIBC), of whom 247 had treatment with mitomycin C (MMC) using Synergo. Nineteen abstracts identified were not included in the evidence review. For full details of the clinical evidence, see section 3 of the assessment report in the supporting documentation on the NICE website.

The 3 pivotal RCTs position Synergo differently in the clinical pathway

3.2 Two RCTs compared treatment with MMC using Synergo with Bacillus Calmette-Guerin (BCG) therapy in intermediate-risk and high-risk NMIBC patients (Arends et al. 2016 and the HYMN trial [Tan et al. 2019]). Arends et al. assessed treatment with Synergo first line, including in people with intermediate-risk cancer who would not normally be offered BCG first line in the NHS. The HYMN trial was a UK-based RCT that included people with NMIBC for which BCG treatment had failed. Colombo et al. (2003 and 2011) compared MMC using Synergo with MMC alone in people with primary or recurrent intermediate-risk and high-risk NMIBC, with 10-year follow-up data.

One RCT showed significantly better disease-free survival with MMC using Synergo compared with MMC alone

3.3 In the trial with a 10-year follow up (Colombo et al. 2011) disease-free survival was significantly better with MMC using Synergo than with MMC alone ($p<0.004$). But there was no significant difference in overall survival ($p=0.558$). The 2 RCTs comparing MMC using Synergo with BCG showed no difference in recurrence-free survival (Arends et al. 2016) or disease-free survival (the HYMN trial). In people with non carcinoma in-situ (CIS) recurrence (papillary tumours only), the HYMN trial showed a non-significant difference in disease-free survival with Synergo compared with BCG (53% compared with 24%; $p=0.11$).

All 3 trials stopped early, which is likely to affect results

3.4 All 3 trials stopped early for various reasons: Colombo et al. because of significantly better efficacy with MMC using Synergo, the HYMN trial because of higher than expected CIS recurrence rate in the Synergo arm, and Arends et al. because of slow recruitment.

All trials used a low-dose adjuvant regimen so some people with CIS may have had treatment that was not effective enough

3.5 All trials only offered an adjuvant regimen (two 30-minute cycles of 20 mg MMC) so 68% of people in the HYMN trial and 22% in Arends et al. with CIS may have not had effective enough treatment. In practice they would have had a higher ablative dose (two 30-minute cycles of 40 mg MMC). Colombo et al. (2003, 2011) included only 1 patient with CIS so most people in this trial are likely to have had treatment with an appropriate regimen. Whether the ablative regimen using Synergo is more effective than other treatment options in people with CIS cannot be determined from the evidence currently available.

The UK-based RCT that best reflected Synergo use in the NHS had substantial limitations

3.6 The HYMN trial was considered to most accurately reflect Synergo use in the NHS. This is because it was a UK-based RCT which included people with NMIBC for whom BCG treatment had failed. The study also included mostly people with high-risk cancer (87%). The EAC noted that the HYMN trial had several issues, which limits the quality and certainty of the results. Not all people in the comparator arm had treatment with BCG. The comparator was BCG or standard care, so some people had treatment with MMC alone or MMC-EMDA (electromotive drug administration of MMC). More people in the Synergo arm had concurrent papillary and CIS tumours, which have a higher risk of recurrence and progression. And the trial did not report on the type of BCG failure before enrolment, although the numbers who had fewer than or more than 6 instillations were reported.

One retrospective comparative study reports post-cystectomy outcomes in people who have had previous treatment with Synergo

3.7 Sri et al. (2020) was a retrospective cohort study that included people who had radical cystectomy for high-risk NMIBC. It compared outcomes between people who had a:

- primary cystectomy, or cystectomy immediately after BCG failure (102 people) and
- cystectomy after treatment with MMC using Synergo, after BCG failure (36 people).

The study reported no significant difference in the time to recurrence or mortality (all-cause and cancer-specific) between the 2 groups. Results suggested that delaying a cystectomy to have second-line treatment with Synergo did not worsen oncological outcomes compared with having the cystectomy straight away and no treatment with Synergo. But relatively few people in the study had treatment with Synergo, and the EAC considered it to

have a high risk of selection bias.

No comparative study looked at high-risk NMIBC alone and no distinction can be made between the results of the different risk groups

3.8 All studies included people with intermediate-risk and high-risk NMIBC and in most cases the results were not reported separately. The extent to which results can be generalised to a high-risk group only is therefore uncertain.

The non-comparative studies were considered to be of low to medium methodological quality

3.9 Fourteen non-comparative studies reported on treatment with Synergo in people with intermediate-risk and high-risk NMIBC. Overall, the non-comparative studies were considered to be of low to medium methodological quality. This was because of, for example, retrospective analyses, small patient numbers, lack of comparators, limited outcomes reported, unclear reporting of risk classifications and, in some cases, uncertainty about whether there was patient overlap between studies. Only 2 were considered prospective studies (Erturhan 2015 and Kiss 2015) and 2 included UK centres (Sooriakumaran 2016; Van Valenburg 2018). There was a high level of heterogeneity in patient characteristics, treatment schedule and follow-up time. Recurrence rates (reported in 13 studies) varied depending on whether an ablative or adjuvant regimen was used, whether patients had had previous BCG treatments, and whether patients had concomitant CIS.

Adverse events appear to be mild to moderate and transient, with few patients stopping treatment because of side effects

3.10 Outcomes related to safety, tolerability and adverse events of Synergo therapy were reported in 18 studies and overall were reported to be mild to moderate and transient with few patients stopping treatment because of side effects. The most

common adverse events during treatment included pain and spasms. After treatment, the most common adverse events were painful or difficult urination (or both), urination at night, and increased urinary frequency. For full details of the adverse events, see section 6 of the assessment report in the supporting documentation on the NICE website.

Cost evidence

The company model only compares treatment with MMC using Synergo and MMC alone

3.11 The company submitted a de novo cost analysis, which compared MMC using Synergo with MMC alone in people with intermediate-risk and high-risk NMIBC, for whom BCG is either unavailable or unsuitable. It used a Markov model comprising 4 health states: remission, recurrence (treated with radical cystectomy in all cases), post-cystectomy, and death. The model had a 1-year cycle length and a lifetime time horizon. The population age was 64 years. BCG was not included in the model as a comparator or as part of the clinical pathway. This was because the company considered it inappropriate to use the available comparative evidence between MMC using Synergo and BCG. Overall, the company's model showed that, compared with MMC alone, treatment with MMC using Synergo was associated with a cost saving of £4,466 per patient over a lifetime time horizon. For full details of the cost evidence, see section 4 of the EAC's assessment report in the supporting documentation on the NICE website.

The company model results are robust but limited by their relevance to the positioning in the clinical pathway

3.12 The company's one-way sensitivity analysis showed that cost saving estimates were most sensitive to changes in the cost of Synergo, the risk of recurrence and the cost of stoma management. None of the variations in parameters made treatment with Synergo cost incurring over a lifetime time horizon.

3.13 The EAC updated the company model and treatment with Synergo was found to

be cost saving by £3,549 per patient over a lifetime horizon. The key drivers of the model were the cost of Synergo, the risk of recurrence, stoma management and the cost of cystectomy. The EAC noted that in the NHS it is unlikely that the decision would be between using MMC with Synergo and MMC alone.

Additional modelling by the EAC shows that MMC using Synergo is likely to be cost incurring compared with second-line BCG

3.14 The EAC did another additional analysis that better reflected current NHS use of the technology by only including people with recurrence of NMIBC after BCG therapy. Treatment with MMC using Synergo was modelled as an alternative to further BCG therapy in people with intermediate-risk or high-risk NMIBC whose disease recurred after intravesical therapy with BCG. The EAC amended the base case model using data from the subgroup analysis of patients without CIS in the HYMN trial (n=33), who were considered to have had treatment with the appropriate dose (adjuvant regimen). Except for costing for BCG therapy instead of MMC alone, all other costs were unchanged. The EAC removed the adverse events costs for MMC using Synergo, because the cost of adverse events was assumed to be similar for MMC using Synergo and BCG therapy. Mortality parameters remained unchanged.

3.15 Compared with BCG as a second-line treatment for patients with no CIS, treatment with MMC using Synergo was associated with an increased cost per patient of £9,858 over a lifetime horizon. Key drivers of the model were treatment costs, annual recurrence rates and starting age. None of the 20% variations in parameters made treatment with MMC using Synergo cost saving over a lifetime horizon.

Treatment with MMC using Synergo is associated with fewer cystectomies and an increase in life years gained and QALYs

3.16 All models resulted in fewer radical cystectomies and an increase in total life years and quality-adjusted life years (QALYs). In the model comparing treatment with MMC using Synergo with MMC alone, the incremental reduction in cystectomies was 0.22 per person and the increases in total life years and QALYs

per person were 2.15 and 2.35, respectively. In the model that compared MMC using Synergo with second-line BCG, these changes were smaller: a 0.02 per person reduction in cystectomies, and a 0.8 and 0.79 increase in the total life years and QALYs per person, respectively.

Exploratory analysis suggests that MMC using Synergo is likely to be cost incurring compared with cystectomy in NMIBC that does not respond to BCG

3.17 The EAC did an exploratory analysis on the cost impact of treating NMIBC that did not respond to BCG with MMC using Synergo compared with radical cystectomy. It was based on the additional modelling for Synergo compared with second-line BCG therapy. It showed that treatment using Synergo was cost incurring by £12,180 per patient compared with cystectomy but was associated with a gain in life years and avoided cystectomy in 4% of people, modelled over a lifetime horizon. For full details, see the addendum to the EAC's assessment report in the supporting documentation on the NICE website.

4 Committee discussion

Position in pathway and unmet need

Treatment options for high-risk NMIBC after BCG failure or when people cannot have or do not want BCG are limited

4.1 The patient and clinical experts said that there are few alternatives to radical cystectomy for people with high-risk non-muscle-invasive bladder cancer (NMIBC) that has not responded to or has recurred after Bacillus Calmette-Guerin (BCG) treatment, or when people cannot have BCG treatment. The clinical experts explained that if people do not want or cannot have a cystectomy, the only options are to have experimental treatment through clinical trials, or cystoscopy every 3 months to monitor disease progression and resection to remove visible tumours. The committee agreed that there is an unmet clinical need for additional treatment options in high-risk NMIBC after BCG failure or when people cannot have or do not want BCG treatment. Mitomycin C (MMC) using Synergo may offer an additional option for these people.

The appropriate place for Synergo in the clinical pathway is for high-risk NMIBC after BCG failure or when people cannot have or do not want BCG

4.2 The clinical experts noted that, compared with MMC alone or BCG therapy, treatment with Synergo requires additional nurse time. This is because a specialist nurse has to accompany the patient throughout the treatment session. Because there are a lot of people with intermediate-risk cancer, or high-risk cancer needing first-line treatment (indicated for BCG), routine use of Synergo in these groups would be resource intensive and it would be difficult to cope with the demand in clinical practice. They agreed that the area with the greatest clinical need, and therefore the most appropriate place for Synergo in the pathway, was as an alternative to further intravesical therapy with BCG or radical

cystectomy for high-risk NMIBC that has not responded to, or recurred after, BCG treatment. The clinical experts said it could also be considered for people who cannot tolerate BCG or who have a contraindication, or if access to BCG is limited. Clinical experts noted that there had been a national BCG shortage in the past and MMC using Synergo was used during this time as an alternative first-line treatment in high-risk NMIBC. The committee concluded that it would base its decision making on using Synergo for high-risk NMIBC that has not responded to or has recurred after BCG treatment, or when people cannot or do not want to have BCG treatment.

Clinical-effectiveness overview

Synergo shows promise but the clinical benefit is uncertain because of limitations in the evidence

4.3 The 3 randomised controlled trials (RCTs) positioned Synergo differently in the clinical pathway and all stopped early. The clinical experts agreed that, of the 3 RCTs, the HYMN trial (a phase 3, multicentre, open-label RCT) best reflected the most appropriate position in the NHS clinical pathway. This is because it included people with recurrence of NMIBC after BCG therapy. However, they explained that a second course of BCG therapy (which was the comparator in the HYMN trial) is not usually offered for high-risk NMIBC that does not respond to BCG. Overall, the committee considered the RCT evidence was not particularly generalisable to these groups because of the comparators in the trials (MMC alone [Colombo et al. 2003, 2011], further BCG therapy [HYMN trial] or MMC-EMDA [Arends et al. 2016]). The trials also had a heterogenous patient population that included people with intermediate-risk and high-risk cancer, different categories of BCG failure, and people with both papillary and carcinoma in-situ (CIS) tumours. And none of the trials involved an appropriate ablative dose for people with CIS tumours, which introduced further uncertainty in this subgroup. Experts advised the committee that CIS tumours differ from papillary tumours and appear to be more difficult to treat. The committee concluded that the clinical benefit at the appropriate position in the NHS treatment pathway was unclear from the available RCT evidence. But, based on expert advice, it agreed that Synergo showed promise.

Synergo after BCG failure does not seem to affect long-term outcomes after radical cystectomy

4.4 A clinical expert said that data published from their NHS centre shows that outcomes (time to recurrence and mortality) are the same after radical cystectomy for people who had treatment with Synergo and people who did not (Sri et al. 2020; see section 3.7). The committee was reassured that offering treatment with Synergo after BCG failure does not seem to affect patients' long-term outcomes.

NHS considerations overview

Appropriate patient selection is important for successful treatment

4.5 The clinical experts said patient selection was important when considering treatment with Synergo. They said that before starting treatment with Synergo, the person should have an up-to-date cystoscopy and repeat transurethral resection of bladder tumour (TURBT) to confirm the absence of residual papillary tumours and ensure the prostatic urethra is free of disease. The clinical experts said that Synergo would not be recommended for cancer that is suspected to have spread outside the bladder or in people with bladder wall diverticulum (a pouch, pocket or sac that protrudes out of the bladder wall). One of the clinical experts said that Synergo may be more effective than suggested by the HYMN trial because of suboptimal case selection in the trial.

Synergo should be delivered in specialist centres by healthcare professionals trained in using it

4.6 The clinical experts said that Synergo should not be delivered in every hospital but in specialised centres only, and offered on a regional cancer network basis. This is because patient selection and treatment require consultants specialised in treating bladder cancer and a dedicated team of bladder cancer nurse specialists trained in using the technology. The clinical experts and company confirmed that

currently treatment with MMC using Synergo is delivered at 5 NHS centres. The patient expert noted that, because access to Synergo is limited to a small number of NHS centres, some people may have to travel long distances for treatment. However, they said that people were willing to travel because there were few other acceptable treatment options available. The patient expert also said that many clinicians do not seem to be aware of Synergo as a treatment option, or are reluctant to offer it if travel is needed. They noted this may disadvantage some people who may be willing to have treatment with Synergo. The clinical experts also explained that the company provides theory-based and practical training with the system. One clinical expert said that their centre has also developed specific in-house training for nurse competency.

Side effects and adverse events

Side effects with Synergo are normally short term and can be managed by a nurse team

4.7 The patient expert said that pain during treatment with Synergo built up over the course of treatment sessions, but that it was possible to learn how to manage the side effects. They said it did not stop them from continuing with treatment. The clinical experts explained that treatment with Synergo is intensive and that side effects vary between people. But they noted they are mostly tolerated and can normally be managed by a dedicated nurse team. The patient and clinical experts also said that the posterior wall of the bladder can be burnt during treatment with Synergo. The clinical experts explained that this is an anticipated side effect of Synergo, is often symptomless and is normally seen during routine follow-up cystoscopies. They said that this reaction appears to resolve without medical treatment. The committee also acknowledged that adverse events and treatment side effects may differ for men and women and that treatment with Synergo is contraindicated in pregnancy.

Caution is needed if a person has implantable cardiac devices or metallic implants

4.8 The clinical experts explained that caution is needed when Synergo is used for people with pacemakers or implantable cardiac devices. They said these people should have a cardiologist involved in their treatment. The company confirmed that there is information on cardiac monitoring for these people in the user manual for the technology. A clinical expert also explained that 1 person with metal in their pelvis had increased pain with Synergo treatment. Metallic implants are also listed as a precaution in the user manual.

Cost modelling overview

Economic modelling is limited by the available clinical evidence and its relevance to the NHS clinical pathway

4.9 The committee accepted the external assessment centre's (EAC) changes to the company model, which showed treatment with MMC using Synergo was cost saving when compared with MMC alone. However, the committee agreed that the modelled clinical scenario comparing MMC using Synergo with MMC alone does not reflect use of the technology in the NHS so has limited relevance. The committee agreed that the additional analysis by the EAC using data from the HYMN trial better reflected current NHS use and that, in this clinical scenario, use of Synergo is likely to be cost incurring. But the committee also noted that the clinical evidence used to populate the model had substantial limitations, which affected the robustness of the model and the certainty of the results. The committee accepted the EAC's additional economic modelling but considered that, because of the uncertainties and the lack of robust clinical data to inform the model, it was difficult to draw firm conclusions about any cost benefits in high-risk NMIBC after BCG failure or when people cannot have BCG.

Model assumptions do not fully capture how all people eligible for Synergo are clinically managed

4.10 The EAC's additional economic model compared MMC using Synergo with second-line BCG. It assumed that everyone who subsequently has a recurrence is offered and accepts cystectomy. The clinical experts said that not all people are fit enough or willing to have surgery, and that these people would normally have repeat cystoscopy and TURBT every 3 months to monitor disease progression and remove recurrent tumours. The clinical experts also noted that some people with a high risk of progression would not be offered further BCG and would be considered for cystectomy instead. The committee understood the difficulties in modelling because of the lack of relevant data, but did not believe an appropriate comparison was made. The EAC explored the cost impact of reducing how many people had a cystectomy for recurrence after intravesical treatment in all models through additional sensitivity analysis. It also did exploratory modelling evaluating the cost of MMC using Synergo compared with cystectomy. It emphasised that these analyses were exploratory only and had several limitations, including uncertainty about the mortality rate for people unable or unwilling to have a cystectomy. The committee concluded that the modelling and assumptions do not fully capture the clinical management of all people eligible for Synergo. Based on the analyses presented at its preferred position in the treatment pathway Synergo was not likely to be cost saving.

In the models Synergo increases QALYs and life years, and reduces radical cystectomies, but the results are uncertain

4.11 The committee noted that in all the models using Synergo resulted in a reduction in radical cystectomies, an increase in total life years and an increase in quality-adjusted life years (QALYs). But the committee concluded that these results were highly uncertain because the models, and the data used to populate them, had limited relevance to the NHS.

Further research

RCTs may not be feasible

4.12 Two of the RCTs for Synergo did not recruit enough people. The clinical experts highlighted the challenges of doing RCTs in a patient population with high-risk cancer after BCG failure or in people who cannot have BCG. The relatively small number of patients per NHS centre for whom BCG had not worked, and who would be eligible for Synergo treatment, makes trial recruitment difficult. Because there are few NHS centres currently offering treatment with Synergo, some people will need to travel for treatment, which would further affect participation in trials. One clinical expert noted that single-arm trials are now being accepted because of the ethical implications of doing RCTs in patients with high-risk NMIBC that has not responded to BCG. The committee accepted the challenges in doing RCTs in this patient population and agreed that further evidence from RCTs may not be feasible.

A retrospective analysis of audit data may provide additional evidence on Synergo use in the UK

4.13 The clinical experts confirmed that all NHS centres using Synergo are required to prospectively collect outcome data in accordance with recommendations set out by NICE interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for NMIBC. The committee concluded that analysing the data collected from UK centres using Synergo may help address the uncertainty in the evidence base. In addition, collecting resource use data will inform a revised cost analysis comparing Synergo to cystectomy or repeat cystoscopies in people who cannot have cystectomy. Outcomes should include bladder preservation rates and bladder cancer-specific mortality.

More information is needed on the additional clinical benefits of inducing hyperthermia using radiofrequency energy

4.14 The committee felt that without more robust evidence of clinical effectiveness,

further information is needed to better understand how Synergo works and if the microwave energy has an additional biological effect beyond heating. The committee understood that the frequency of radiofrequency used by the Synergo system (915 MHz) is an unlicensed and safe frequency used in radiocommunication. The company explained that preclinical data showed a direct and selective effect of radiofrequency on cancer cells. It also said that studies showed increased concentrations of MMC in the bladder wall of people having treatment with Synergo. The committee noted there are other device-assisted chemotherapy options currently used in the NHS. In particular, conductive hyperthermic intravesical chemotherapy, which heats the circulating chemotherapy drug outside the bladder. The committee was aware that published evidence on the efficacy of other device-assisted chemotherapy options is limited at present. However, it agreed that information on the benefits and costs of Synergo, compared with other device-assisted chemotherapy technologies available in the NHS, could improve clinical decision making.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technologies advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology assessment analysts (who act as technical leads for the topic), a health technology assessment adviser and a project manager.

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Update information

Minor changes since publication

December 2025: Medical technologies guidance 61 has been migrated to HealthTech guidance 601. The recommendations and accompanying content remain unchanged.

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