National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT496 Leukomed Sorbact for preventing surgical site infection

Consultation comments table

Final guidance MTAC date: 13 November 2020

There were 15 consultation comments from 3 consultees:

- 1 representative of the company
- 2 representatives from professional organisations

The comments are reproduced in full, arranged in the following groups – wording, recommendation, bias in the clinical evidence, relevant clinical evidence, recommendations for all types of surgery, equalities, other.

#	Consultee ID	Role	Section	Comments	NICE response DRAFT/FINAL
	Wording				
1	1	Company	4.5	This reads as though the increase in mean hospital stay was associated with Leukomed Sorbact; this wasn't the case. We would suggest this is re-phrased to read "developing SSI led to an increase in mean hospital stay of 8.2 days in the control group, and patients in the Leukomed Sorbact group had more outpatient visits (4.6. vs. 2.9 per person).	Thank you for your comment. The committee amended the wording in section 4.5 to “developing SSI led to an increase in mean hospital stay of 8.2 days in the control group. People in the

					Leukomed Sorbact group with an SSI had more outpatient visits compared to people with an SSI in the control group (4.6 per person compared to 2.9 per person, respectively)".
2	1	Company	4.15	This currently reads: SSI episode cost: base cost £362, breakeven point £4048. We would suggest that this should read: SSI episode base cost £4048, breakeven point £362	Thank you for your comment. The committee amended section 4.15 to "SSI episode cost: base case £4,048, breakeven point £362"
3	2	Professional organisation	4.1	Disagree. The evidence does not support this claim. It MAY reduce the incidence of SSIs....	Thank you for your comment. The committee reviewed the evidence and decided not to amend the wording. Please see NICE's response to comments 9 and 10 for further detail about the evidence review.
4	2	Professional organisation	4.2	The evidence does not support this claim. It MAY reduce the incidence of SSIs	Thank you for your comment The committee reviewed the evidence and decided not to amend the wording Please see NICE's response to comments 9 and 10 for further detail about the evidence review.

	Recommendation				
5	2	Professional organisation	1.3	This is questionable given the quality of the evidence in relation to clinical effectiveness - please see more detailed comments below.	Thank you for your comment. Please see NICE's response to comments 9 and 10 for further detail about the evidence review
6	2	Professional organisation	1.1	Disagree that the evidence is sufficiently robust to support widespread implementation of this product for these types of wounds Please see rationale for this below.	Thank you for your comment. The committee were confident that the evidence was of sufficient quality, quantity, and consistency to make its recommendations, based on the clinical and economic evidence and were informed by contributions from expert advisers. Please see NICE's response to comments 9 and 10 for further detail about the evidence review
7	2	Professional organisation	1.2	Disagree - insufficiently robust evidence to support widespread use. Please see rationale for this in comments below.	Thank you for your comment. The committee were confident that the evidence was of sufficient quality, quantity, and consistency to make its recommendations, based on the clinical and

					economic evidence and were informed by contributions from expert advisers. Please see NICE's response to comments 9 and 10 for further detail about the evidence review.
8	3	Professional organisation	General	3. Are the recommendations sound and a suitable basis for guidance to the NHS? Based on our exploration of the data presented in response to question 2, we believe that the evidence that Leukomed Sorbact reduces the risk of SSI is of low or very low certainty, depending on the indication being considered, and insufficient to make a recommendation for use following C-section in the UK and extremely limited in relation to vascular surgery. Given the cost for Leukomed Sorbact is £182.92 excluding VAT for a pack of 20 (NHS supply chain price from EAC report) we would argue that higher certainty clinical evidence is required to justify an adoption recommendation. Furthermore, such a recommendation in the absence of high certainty evidence will prevent further, high quality research of the effects of Leukomed.	Thank you for your comment The committee recognised that there are uncertainties in the clinical evidence that are described in the guidance but considered the economic evidence to be reasonable within the context of the clinical evidence and the expert advice. The committee amended section 4.2 to acknowledge the limitations of the evidence. Text was added to section 4.2 and 4.17 to welcome further research, including RCTs and real-world evidence collection, for the use of Leukomed Sorbact after vascular surgery. Please see NICE's response to comments 9 and 10 for further detail about the evidence review.

	Bias in the clinical evidence				
9	2	Professional organisation	4.1	a limited risk of bias The risk of bias appears to have been under-estimated. An attrition rate of almost 10% (almost the same as the number of reported SSI events) mean that there is a high risk of bias. In addition, as SSI is a subjective judgement (and there was no blinded outcome assessment) , and there was only 14 day follow up, rather than the recommended 30 day follow up, detection bias is likely. Therefore, risk of bias may be greater than is suggested and it is likely that there is only low certainty evidence that Leukomed Sobact reduces SSI in this patient population. We welcome further review of the evidence, to consider this feedback.	Thank you for your comment The committee heard from the EAC how the risk of bias was assessed using version 2 of the Cochrane risk of bias tool (RoB2), a study level assessment tool. A table was included in the assessment report to outline the assessment of the clinical evidence. The EAC assessment report addresses the 9.3% attrition rate in Stanirowski et al. 2016a. The committee were advised that the attrition rate in this case is comparable or lower than that of other studies and the study is still adequately powered after taking attrition into account. The EAC explained to the committee that Stanirowski et al. 2016a reports that outcome assessors were blinded. The committee heard that a 14 day follow up period is shorter than the Centre for Disease Control and Prevention (CDC) definition

					of surgical site infection. However it was also advised that the literature reports that SSIs that happen after a C-section are typically superficial and thus in the vast majority of cases present within 14 days. The committee acknowledged that although 14 days follow up is not ideal, it may be a reasonable amount of time to assess the impact of this intervention. The committee considered all the points raised in the comment alongside expert advice and responses from the EAC. It concluded that the risk of bias had been appropriately assessed and their interpretation of the evidence remained unchanged.
10	3	Professional organisation	General	2. Are the summaries of clinical and resource savings reasonable interpretations of the evidence? Our Response: To consider this question we looked separately at the evidence for the C-section population (three studies) and the vascular surgery population (two studies). In each case we re-looked at the evidence included in the Guidance and applied GRADE where possible to consider evidence certainty for the outcome of SSI.	Thank you for your comment The committee heard from the EAC how the risk of bias was assessed using version 2 of the Cochrane risk of bias tool (RoB2), a study level assessment tool. The EAC considered RoB2 the most appropriate assessment tool for this guidance because an

				2.1 Risk of bias assessments and use in the GRADE process For our risk of bias assessment we requested additional information from the author of two included RCTs [1,2]. We contacted this author because the randomisation processes as reported had the potential to be quasi-randomised. Author responses reassured us that the approach used to generate the randomisation sequence is probably acceptable, but that allocation concealment is at best unclear and may be high risk of bias. We assumed unclear for our assessment. We did however, consider that the lack of blinding of outcome assessors in all RCTs and the attrition bias in the RCTs in women having C-sections constitute high risks of bias. In this respect we differ from the EAC. We consider that SSI is a subjective outcome so detection bias is an issue; we also consider that where the number of participants lost to follow up is close to the number of events attrition bias should be considered a risk. In our GRADE assessment for the risk of bias domain we adopted a conservative approach and did not downgrade for performance bias because of the nature of the intervention. We further implemented a conservative approach by applying a single (rather than dual) downgrade for the two other risks of bias in the C-section RCTs, as the attrition bias formed part of our assessment of the impact of imprecision on the certainty of the effect estimate.	assessment of the quality of individual studies is better considered alongside the economic evidence and expert advice. The EAC assessment report addresses the 9.3% attrition rate in Stanirowski et al. 2016a. The committee were advised that the attrition rate in this case is comparable or lower than that of other studies and the study is still adequately powered after taking attrition into account. The EAC explained to the committee that Stanirowski et al. 2016a reports that outcome assessors were blinded. However, they highlighted the lack of full blinding in the rest of the studies as a limitation. The committee heard from the EAC and from experts that the clinical evidence for vascular surgery is underpowered to detect a statistical difference in the primary outcome. The committee amended the wording to section 4.2 of the guidance to acknowledge the limitations of the evidence.

				2.2 Data for women undergoing C-section - Analysis and application of GRADE For these data we undertook an exploratory analysis which looked at the pooled estimate of the trials Stanirowski 2016a [1] and Stanirowski 2016b [2]. A random effects analysis produced a relative risk (RR) of SSI of 0.33 (95% CI 0.14 to 0.77) based on the completed case analyses. However, the evidence is low certainty, because it is downgraded once for imprecision and once for risk of bias (across more than one domain). The reason for downgrading for imprecision is because, although there were over 680 participants, the number of events is very small; even a small change in the number of infections in one arm would be sufficient to produce a considerable difference in the effect estimate. This issue holds for each study individually as well as when pooled. The fact that there was a considerable degree of attrition bias (almost 10% of participants across the two trials – more people than the number of reported events) has the potential to add to this issue. Imputation with a best case scenario (no SSI in women lost to follow-up and excluded from analysis) produces an effect estimate aligned with a completed case analysis but imputation with a worst case scenario (where women lost to follow-up were assumed to have an SSI) produces a very different result. This is low certainty evidence that there may be a lower incidence of SSI in women treated with Leukomed Sorbact compared with women treated with standard dressings following caesarean section.	The committee considered the points raised in the comment and decided the recommendation should remain unchanged. The committee amended section 4.2 to acknowledge the limitations of the evidence. Text was added to section 4.2 and 4.17 to welcome further research, including RCTs and real-world evidence collection, for the use of Leukomed Sorbact after vascular surgery. The committee concluded that the limitations of the evidence had been appropriately assessed and that the study results and plausibility of clinical benefit was sufficient to support the use of Leukomed Sorbact after vascular surgery and caesarean section.

				All trials used Center for Disease Control (CDC) definitions for SSI but the trials in the C-section population only had follow up for 14 days instead of the usual 30, potentially missing later developing infections. This seems a possible source of indirectness of relevance; the EAC noted that the RCTs in women undergoing C-sections took place in a non-National Health Service (NHS) (European Union-27) setting which may impact relevance to NHS context. 2.3 Vascular surgery - Analysis and application of GRADE The reported RR in the RCT that recruited people having vascular surgery is 0.63 (95% CI 0.33 to 1.21) (the paper presents an OR). Again the number of events is low: the effect is based on 12 events in the experimental group compared to 18 in the control group (total number of people in the ITT analysis is 162); the confidence intervals include the possibility of increased infections in the Leukomed Sorbact arm, as well as no difference or benefit to the intervention. We judge the evidence for the relative effectiveness of this innovation on SSI risk to be of very low certainty, meaning it is uncertain and the true effect is probably markedly different from the effect estimate. We downgraded the certainty of the evidence twice for issues of imprecision and once for high risk of bias (detection bias). We only considered the evidence from the RCT in this assessment but while the precision around the effect estimate would be increased by considering the non-randomised study so would the risk of	

				bias; the certainty of the evidence would still be very low, meaning that we are uncertain what the effect of the intervention is on SSI in people undergoing vascular surgery	
	Relevant clinical evidence				
11	2	Professional organisation	4.2	the study results and the plausibility of the clinical benefit for this group was sufficient to support the use of Leukomed Sorbact after vascular surgery. Again, the number of events is low and the reported confidence intervals include the possibility of more infection in the Leukomed Sorbact arm. Therefore, it is likely that there is only low or very lower certainty evidence, insufficient to support widespread adoption of this product. We would welcome further review of the evidence.	Thank you for your comment Please see NICE's responses to comments 9 and 10.
12	3	Professional organisation	General	"This draft guidance relates to the use of Leukomed Sorbact for the prevention of surgical site infection (SSI) in closed surgical wounds (wounds which are healing by primary intention) and which have low to moderate levels of exudate. Technology: Leukomed Sorbact is described as a sterile, single-use, bacteria-binding, adhesive-bordered, wound dressing. The innovative component of the dressing is the absorbent non-woven wound contact pad. This is coated with dialkylcarbamoyl chloride (DACC). This is stated to bind hydrophobic bacteria and fungi meaning that they are removed from the wound environment at dressing change. This binding and inactivation process is stated to reduce colonisation of the wound by	Thank you for your comment The committee heard from the EAC how the risk of bias was assessed using version 2 of the Cochrane risk of bias tool (RoB2), a study level assessment tool. The EAC considered RoB2 the most appropriate assessment tool for this guidance because an assessment of the quality of individual studies is better considered alongside the economic evidence and expert advice. The committee acknowledged the merits of GRADE as a

				potentially harmful microbes and hence reduce the incidence of SSI Population: intended for use in people with closed surgical wounds (wounds healing by primary intention) which have low to moderate levels of exudate. Comparators: are defined as conventional post-surgical wound dressings or negative pressure wound therapy (NPWT). Outcomes considered are: SSI; dehiscence; abnormal scarring; the ASEPSIS wound score, (additional treatment, serous discharge, erythema, purulent exudate, separation of tissues, isolation of bacteria, stay duration as an inpatient); length of stay (postoperative) in hospital relating to SSI; readmission related to SSI; time until full wound closure; prescription and dose of antibiotics; patient pain and discomfort; condition specific and generic quality of life measures; outpatient clinic attendances; post-operative mortality rate; device related adverse events. These are listed in the order they are detailed in the External Assessment Centre (EAC) report; SSI may be considered the primary outcome due to the focus of the decision problem. Only a minority of these outcomes were assessed in the identified RCTs. Draft recommendations: • That the evidence supports the case for adopting Leukomed Sorbact for closed surgical wounds after caesarean section and vascular surgery in the NHS	tool to rate the body of evidence at the outcome level rather than the study level.

				• That Leukomed Sorbact should be considered as an option for people with wounds expected to have low to moderate exudate; it should be used as part of usual measures to reduce the risk of SSI. • That the reduced rate of SSI with Leukomed Sorbact compared with standard surgical dressing leads to savings of o £107.43 per person after caesarean section o £17.82 per person after vascular surgery Evidence presented The EAC considers five studies. Firstly three studies in women undergoing C-sections - a randomised controlled trial (RCT) [1], a pilot RCT [2], and a study described as an unpublished audit (details redacted but appear to relate this material [3,4], if so, not a controlled study). Whilst the two RCTs are from the same team and have very similar methods the reported recruitment periods do not overlap suggesting that the pilot data are not a sub-set of the main trial data. Secondly, two studies are in people who have undergone vascular surgery (non-implant) [5,6]. One study is described as a pilot RCT [5] and the other [6] comparison with a non-contemporaneous control (first 100 participants given one treatment, second 100 given alternative). There is no meta-analysis in the Guidance. CONSULTATION RESPONSE	

				To address the questions asked in the consultation we undertook a rapid literature search including assessing the references of an identified systematic review.[7] We identified relevant studies based on the PICO above and then extracted key aspects of study characteristics and outcome data. Where appropriate we undertook statistical pooling of the studies using a random effects meta-analysis with exploratory analyses of the effect of imputation of missing data. We performed a risk of bias assessment on the identified RCTs using the Cochrane risk of bias tool [8] and then undertook a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment [9] of the certainty of the evidence for each indication for the outcome of SSI. GRADE considers the risk of bias together with the imprecision, indirectness and inconsistency of a specific result; publication bias is also considered. Our use of GRADE is in contrast to the focus on statistical significance in the current draft Guidance. GRADE provides a more complete and transparent method of considering the quality of available evidence, in turn influencing how it is used to support decision making and recommendations for practice. The consultation asks that we consider the following questions 1. Has all of the relevant evidence been taken into account? Our Response:	

				We did not identify any additional evidence directly relevant to the question; in particular we did not identify any additional RCTs that evaluated the product in people with closed surgical wounds.	
	Recommendation for all types of surgery				
13	2	Professional organisation	4.3	Agree!	Thank you for your comment
	Equalities				
14	3	Professional organisation	General	4. Are there any equality issues that need special consideration and are not covered in the medical technology consultation document? No response	Thank you for your comment
	Other				
15	3	Professional organisation	General	References 1. Stanirowski PJ, Bizon M, Cendrowski K, Sawicki W. Randomized controlled trial evaluating dialkylcarbamoyl chloride impregnated dressings for the prevention of surgical site infections in adult women undergoing caesarean section. Surgical Infections 2016a; 17 (4): 427-35 2. Stanirowski PJ, Kociszewska A, Cendrowski K, Sawicki W. Dialkylcarbamoyl chloride-impregnated dressing for the prevention of surgical site infection in women undergoing caesarean section: a pilot study. Archives of Medical Science 2016b; 12 (5): 1036-42 3. Taylor L, Mills E, George S, Seckam A. Reducing SSI rates for women birthing by caesarean section Journal of Community Nursing 2020; 34 (3): 50-53	The MTEP team received one comment which presented several comments for consideration that were better addressed when split into the relevant themes, with agreement of the consultee. The references included in comment 15 are relevant to comments 8, 10, 12 and 14.

				4. Woodhouse L, Taylor L, Mayes J. Surgical site infection; positive outcomes through continuity of care. https://www.jcn.co.uk/files/files/JCN-FB-Live-15-July-2020-SSIs.pdf 5. Totty JP, Hitchman LH, Cai PL, Harwood AE, Wallace T, Carradice D et al. A pilot feasibility randomised clinical trial comparing dialkylcarbamoylchloride-coated dressings versus standard care for the primary prevention of surgical site infection. International Wound Journal 2019; 16 (4): 883-90 6. Bua N, Smith GE, Totty J, Pan D, Wallace T, Carradice D et al. Dialkylcarbamoyl chloride dressings in the prevention of surgical site infections following non-implant vascular surgery. Annals of Vascular Surgery 2017; 44: 387-92 7. Totty J, Bua N, Smith GE, Harwood AE, Carradice D, Wallace T et al. Dialkylcarbamoyl chloride (DACC)-coated dressings in the management and prevention of wound infection: A systematic review. Journal of Wound Care 2017; 26 (3) 107-14 8. Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from www.training.cochrane.org/handbook. 9. GRADE Working Group (2013). GRADE Handbook. Handbook for grading the quality of evidence and the strength of	

				recommendations using the GRADE approach. H. Schünemann, J. Brożek, G. Guyatt and A. Oxman."	

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