NICE National Institute for Health and Care Excellence

NICE guidance

Prontosan for treating acute and chronic wounds

Medical technologies guidance
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www.nice.org.uk/guidance/mtg67

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 MIB220.

1 Recommendations

1.1 More research is recommended on Prontosan for treating chronic wounds. There is some evidence that it is clinically effective but not enough to recommend it for routine use. Prontosan is not recommended for treating acute wounds because the evidence is very limited.

1.2 Research should be a randomised controlled trial on the effectiveness of Prontosan compared with saline or water in chronic wounds of different types. Wounds should be followed up until completely healed, and time to healing should be measured. Find out more details in further research.

Why the committee made these recommendations

Care of acute or chronic wounds aims to improve their condition, help with healing and minimise risk of complications. Usually, wounds are cleansed with saline or water.

Prontosan is available in 3 different formats: a solution, a gel, and extra thick gel. The solution is used for rinsing and soaking wounds. It can be used alone or with one of the gels. After soaking, the gel can be applied to the wound and left in place until the next dressing change. It aims to prevent build-up of microbes such as bacteria in the wound to help with healing.

Most of the evidence about Prontosan's effectiveness is not of good quality. It may speed up wound healing and reduce infections compared with saline in chronic wounds, but more evidence is needed to confirm this. There is very little evidence about using Prontosan for treating acute wounds.

Cost analyses suggest that Prontosan is cost saving compared with saline in chronic wounds. But there is not enough good quality evidence about its clinical effectiveness, which limits how reliable the cost analysis is. So, more research is recommended to address the uncertainties.

2 The technology

Technology

2.1 Prontosan (B Braun) is a range of topical solutions and gels used for cleansing, rinsing and moistening acute and chronic wounds. Prontosan includes:

- Prontosan Wound Irrigation Solution, which is used for rinsing wounds or applied to gauze as a soak. It is available as a 350 ml bottle, as 40 ml single-use pods and as a 1,000 ml bottle for instillation.
- Prontosan Wound Gel, which is applied to the wound bed after cleansing, during dressing changes and before further dressings are applied. It is available as a 30 ml bottle. It can be used in deep and tunnelling wounds, wound cavities or wounds that are difficult to access.
- Prontosan Wound Gel X (extra thick gel), which is applied in the same way as the Wound Gel. It is available as a 50 g or 250 g tube. It can be used in flat wounds or wounds with a large surface area, such as leg ulcers.

2.2 Prontosan received a CE mark in February 2009 as a class 3 medical device. The CE mark covers the Prontosan solution and gels.

Innovative aspects

2.3 The solution and gels contain an antimicrobial polyhexanide (0.1% polyhexamethylene biguanide) and a betaine surfactant (0.1% undecylenamidopropyl betaine). Prontosan is the only wound cleansing solution or gel that contains these 2 active ingredients. The company claims they work together to prevent biofilm forming in the wound bed and break it down if it has formed. The company claims that it cleanses and removes slough, devitalised tissue and other wound debris.

Intended use

2.4 Prontosan is intended for cleansing, rinsing or moistening acute and chronic wounds. It can be used by healthcare professionals in community and acute care settings, such as outpatient clinics, hospital inpatient care, GP surgeries, postoperative care and at the patient's home. The company states that brief training may be needed, but this is likely to be unnecessary for staff who are already trained in cleansing wounds with saline or water.

Costs

2.5 Prontosan is available in several forms, quantities and costs:

- Prontosan Wound Irrigation Solution: £5.03 for a 350 ml bottle (cost per dressing change £0.57); £0.62 per 40 ml ampoule
- Prontosan Wound Gel: £6.71 for 30 ml
- Prontosan Wound Gel X: £12.29 for 50 g (cost per dressing change £2.51); £32.89 for 250 g (cost per dressing change £1.34).

  For more details, see the website for Prontosan.

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 18 studies

3.1 The evidence assessed by the EAC included 18 studies. Seventeen were full-text peer-reviewed publications and 1 was an unpublished study. Of the included studies, 9 were comparative studies (7 randomised controlled trials and 2 observational studies) and 9 were non-comparative observational studies. The comparative evidence included a total of 792 people, of which 415 had Prontosan, 281 had saline, 53 had saline or Ringer's solution, 23 had silver sulfadiazine, and 20 had sterile water. For full details of the clinical evidence, see section 4 of the assessment report in the supporting documentation for this guidance.

There are weaknesses in the evidence with only 1 study at low risk of bias

3.2 The EAC considered the strength of the evidence to be limited, with only 1 randomised controlled trial at low risk of bias. Five randomised controlled trials had some methodological concerns. The remaining studies were considered to be at high risk of bias. Further limitations of the evidence base included the following points:

- Most of the included studies had small sample sizes and some of the larger randomised controlled trials were underpowered (meaning they do not have enough people in them to draw meaningful conclusions). However, the EAC noted that larger sample sizes might not be achievable.

- Prontosan use varied across the studies. For example, in 3 studies Prontosan solution was used only once, to irrigate the wound. In 4 studies only the gel was used. It was not always used in a way that reflects NHS practice, or in line with the company's instructions for use.
- Outcomes were not always clearly reported and similar outcomes were reported differently across different studies. This made it difficult to make comparisons and draw conclusions across the evidence base.

The evidence for different types of chronic wounds was varied with 3 comparative and 7 non-comparative studies

3.3 Ten studies included different subgroups of chronic wounds, for example, venous leg ulcers, vascular ulcers, pressure ulcers, arterial leg ulcers, diabetic foot ulcers, burns, trauma wounds and surgical wounds). These included 2 randomised controlled trials (Bellingeri 2016; Valenzuela 2008), 1 comparative cohort study (Assadian 2018) and 7 non-comparative studies (Atkin 2020; Ricci 2018; Moore 2016; Durante 2014; Moller 2008; Horrocks 2006; Oropallo, 2021). Bellingeri 2016 was at low risk of bias, but the study was underpowered based on its own statistical analysis plan. It was also potentially at risk of selective reporting. Clinical experts advised that Prontosan gel may not be used at every dressing change and depends on the clinical assessment of the wound (For full details of the cost evidence, see section 4.2 of the assessment report in the supporting documentation for this guidance). Valenzuela 2008 used the gel only. Assadian 2018 had a small sample size and had limited applicability to the NHS because only a single application of Prontosan was used. Reported outcomes included wound healing, wound bed condition, wound infection, pain, dressing changes and quality of life.

There are 4 comparative studies for venous leg ulcers

3.4 Four studies were included for venous leg ulcers: 3 randomised controlled trials (Borges 2018; Harding 2012, unpublished; Romanelli 2010) and 1 comparative retrospective analysis (Andriessen 2008). All 3 randomised controlled trials had a small sample size and may have been underpowered. The control group in Andriessen 2008 had either

saline or Ringer's solution. The clinical experts advised the EAC that Ringer's solution is not routinely used in the NHS to cleanse venous leg ulcers. Reported outcomes included rate of wound healing, time to wound healing, wound size, wound infection and factors associated with wound infection (bacterial burden and number of microorganisms) and pain.

There is limited evidence for burn wounds with no NHS comparators

3.5 Only 3 studies were included for burns: 1 randomised controlled trial (Wattanaploy 2017) and 2 non-comparative studies (Ciprandi 2018; Kiefer 2018). The sample size in the randomised controlled trial was small, saline was used in both arms, and the comparator was silver sulfadiazine. This was not considered to be standard care in the NHS so was not included in the scope for this guidance as a comparator for Prontosan. However, silver sulfadiazine is indicated for prevention and treatment of infection in burns. Reported outcomes included wound healing, wound infection, pain and treatment satisfaction. No significant differences were found for healing burn wounds and improving wound infection with Prontosan compared with silver sulfadiazine (Wattanaploy 2017).

There is limited evidence for surgical site wounds

3.6 Only 1 study, a randomised controlled trial, was included for surgical site wounds (Saleh 2016). This study had a small sample size, and the comparator was sterile water. The EAC included this study because surgical site wounds were considered relevant to the decision problem. The EAC noted that although the study compared Prontosan with dressings soaked with sterile water, only one dressing was applied after surgery. This treatment approach may have limited applicability to the NHS. The study outcomes included wound infection but not wound healing. The study reported a statistically significant higher rate of infection in the Prontosan group compared with the sterile water group.

It is not certain if Prontosan has better outcomes than saline

3.7 In total, 6 randomised controlled trials and 1 comparative retrospective analysis compared Prontosan with saline. Wound healing was reported in 2 studies (Harding 2012, unpublished; Andriessen 2008), wound size in 3 studies (Romanelli 2010; Valenzuela 2008; Harding 2012, unpublished) and wound condition improvement in 2 studies (Bellingeri 2016; Valenzuela 2008). Of these 4 studies, 2 showed statistical significance in wound improvement (Bellingeri 2016; Valenzuela 2008). Infection rate was reported in 2 studies (Harding 2012, unpublished; Andriessen 2008), bacterial burden in 2 studies (Assadian 2018; Romanelli 2010), bacterial load in 1 study (Borges 2018), inflammation score in 1 study (Bellingeri 2016), and microbiological cultures and redness around the skin (a clinical sign of infection) in 1 study (Valenzuela 2008). Of these 6 studies reporting on wound infection and associated factors, only 3 showed a statistically significant reduction in:

- bacterial burden (Romanelli 2010)
- inflammation score (change in inflammatory signs; Bellingeri 2016)
- microbiological cultures and redness around the skin (Valenzuela 2008).

Pain was reported in 4 studies (Bellingeri 2016; Harding 2012, unpublished; Romanelli 2010; Valenzuela 2008). Only 1 study found a significant reduction in pain when using Prontosan (Romanelli 2010). The EAC concluded that Prontosan appeared to be effective for some clinical parameters in chronic wounds, but there is not enough good quality comparative evidence with saline.

Prontosan is safe and easy to use

3.8 Prontosan is safe, provided clinical staff are aware of the contraindications outlined in the instructions for use. Adverse events are rare and easily managed. The products are easy to use and the clinical experts said that minimal training is needed. Training resources are available from the company.

Cost evidence

The company's cost modelling finds Prontosan to be cost saving

3.9 The company submitted 2 de novo cost analyses with different model structures. One used a Markov model (wound closure model) that compared costs for Prontosan with saline to treat venous leg ulcers until full wound closure. The time horizon was 1 year. The clinical experts advised the EAC that when using Prontosan, wounds healed within a year. The company provided 2 alternative data sets for rate of wound healing for this model (Andriessen 2008 and Harding 2012, unpublished). The other model was a simple cost model (wound bed preparation model) that compared costs for Prontosan with saline to treat chronic wounds (for example, leg ulcers and pressure ulcers) until the wound bed is fully granulated. This means that there are visible signs that the wound is healing. The time horizon used was the time to reach a Bates-Jensen wound assessment tool (BWAT) score of 14. The BWAT score is a clinical tool used for scoring wound healing. The time taken to reach a score of 14 was 4.1 weeks for Prontosan and 11.3 weeks for saline (Bellingeri 2016). The company reported base-case cost savings per person with Prontosan of £1,118.26 and £1,188.47 for the wound closure model (with data from Andriessen 2008 and Harding 2012, unpublished, respectively) and £1,134.40 for the wound bed preparation model. The key drivers for cost savings in both models included reduced:

- time to healing or time to wound bed improvement
- costs of healthcare visits
- time in infected state.

For full details of the cost evidence, see section 9 of the assessment report in the supporting documentation for this guidance.

The EAC agrees with the company's cost models but the key limitation is that the clinical evidence is uncertain

3.10 The EAC agreed with the structure of both of the company's models and

its assumptions and made minor alterations to the costs and resource use. This had little impact on the cost savings (for full details see section 9 of the assessment report in the supporting documentation for this guidance). The EAC noted that the inputs for wound healing and infection rates in the wound closure model were uncertain, as were the inputs for wound bed improvement in the wound bed preparation model. The EAC acknowledged uncertainty in the cost modelling but noted that the approach was conservative. It made the following comments:

- Andriessen (2008) is a retrospective comparative case series of 112 patients with venous leg ulcers with a follow-up time of 6 months. The EAC considered that Andriessen 2008 was a suitable data source because of the larger number of patients and longer follow up. However, the study was at high risk of bias because of potential selection and reporting bias.
- Harding (2012) is a small, unpublished, UK pilot randomised controlled trial with 34 patients. The shorter follow-up period of 12 weeks meant that there was greater reliance on extrapolation for the calculation of transition probabilities for wound healing. There were some concerns about the randomisation process.
- Bellingeri (2016) is a randomised controlled trial of 289 patients with pressure ulcers or vascular leg ulcers at low risk of bias. The follow up was 28 days, and wounds were assessed using the BWAT score. The company used an Excel trendline to extend the graphs to reach a mean BWAT score for both arms. However, there were concerns about the data. The study seemed to use only 8 out of the 13 dimensions of the BWAT. This meant the overall score was not on a scale of 13 to 65, but on a scale of 8 to 40. As a result, the EAC could not be confident that a reported BWAT score of 13 or 14 in Bellingeri (2018) accurately corresponded to a wound approaching healing or one that has healed. However, no improved data source has been identified.

The EAC base case uses the wound closure model with inputs from Andriessen 2008 and estimates a cost saving of £951 per person

3.11 The EAC considered that the wound closure model with clinical inputs from Andriessen 2008 was the most appropriate base case. It concluded

that Andriessen 2008 was the most suitable data source and provided the most robust estimates for wound improvement, deterioration and recurrence that reflected the clinical reality of treating chronic wounds. This model estimated a cost saving from the use of Prontosan compared with saline of £951 per patient over a time horizon of 1 year.

4 Committee discussion

Clinical effectiveness overview

Prontosan shows promise but there is not enough evidence of its clinical benefit

4.1 The committee noted that much of the evidence comparing Prontosan and saline in treating chronic wounds had some concerns or was at high risk of bias. The committee noted that there was very limited evidence for acute wounds. The committee agreed that the technology showed promise based on clinical expert advice, but that this was not supported by the evidence. The committee concluded that there was not enough good quality evidence to make a clear judgement about the benefits of Prontosan compared with saline or water.

The evidence is heterogeneous in terms of wound type

4.2 The committee noted that the patient populations in the evidence were heterogeneous, including different wound types such as venous leg ulcers, chronic wounds of mixed aetiology, burns and surgical site wounds. The clinical experts agreed that Prontosan could be used for a broad patient population. Some experts suggested that chronic wound management approaches are likely to be similar in the basic principles of dressing management, despite differences in the underlying causes and treatment. Nevertheless, the committee understood that there is a diversity of wound types in the chronic wound population and that it is difficult to generalise the evidence from the trials to the total population with chronic wounds. Ideally, further evidence is needed to detect clinically meaningful results in specific wound types (for example, pressure ulcers or venous leg ulcers).

How Prontosan products are used in the studies varies but this is likely to reflect NHS practice

4.3 The committee noted that how Prontosan products were used ranged across the studies. Prontosan solution was used alone, with the gel or gel X, or the gel or gel X were used alone. The clinical experts agreed that the choice of Prontosan product used depends on the wound and the person's situation. The clinical experts said that the Prontosan solution is used as a soak for chronic wounds. Soak times can vary between 5 and 15 minutes depending on the wound condition and size. Guidelines recommend using cleansing solutions such as Prontosan during dressing changes. For example, during consultation, the committee was made aware of the National Association of Tissue Viability Nurse Specialists (Scotland) wound cleansing pathway which recommends: 'if the wound is chronic, infected, have debris or residual dressing in place OR if the patient is at high risk of wound infection, consider using a biofilm disrupting cleansing solution'. The committee also noted that the National Wound Care Strategy Programme's lower limb recommendations recommend cleansing the wound bed at each dressing change. The clinical experts noted that the gel is used less often, and almost always in combination with the solution to support and maintain the soak process. The clinical experts said the gel is most often used for more complex and chronic wounds and for people with a history of recurrent infections. The clinical experts agreed that both the solution and gel have the same ingredients and should be considered the same product. The committee recognised the heterogeneity in the way the Prontosan products were used but concluded there may also be differing approaches used in the NHS.

Prontosan has plausible benefits

4.4 The clinical experts noted that, in their experience, using Prontosan on static (non-healing) chronic wounds with a dull brown colour causes the wound bed to change to vibrant red granulated tissue (tissue in the process of healing). No adverse events or allergic or instant reactions to Prontosan were observed by the clinical experts. The clinical experts said that Prontosan is easy to use, soothing and does not sting. The committee recognised that patient reported outcomes such as pain and

odour are important considerations when treating chronic and acute wounds and concluded that Prontosan has plausible benefits.

Outcome measures

Complete wound healing is the preferred outcome

4.5 The clinical experts said that they would use Prontosan when clinically indicated, typically until the wound bed was completely clean and looking healthy and epithelised (when a layer of new tissue forms over the wound). The clinical experts clarified that wounds can epithelialise and close, but this does not mean the wound is healed. For people with a history of recurrent infection, the wound can break down again if treatment is stopped before the wound is healed. Some types of chronic wounds, specifically leg ulcers, often deteriorate and recur. To measure Prontosan's effectiveness compared with saline, the committee concluded that evidence is needed that follows wounds until they are completely healed. This evidence should also measure the time it takes for complete healing to happen.

Improved wound bed condition is an important outcome

4.6 Chronic wounds can be complex and may become static or have high levels of recurrence. The clinical experts noted that some people have wounds for several years and some may never heal. The experts agreed that improved wound bed condition is an important outcome. Wounds move through different stages of healing. Unless the wound bed is prepared through debridement, removing slough and clearing biofilm, the wound becomes stagnant and cannot heal. Improving wound bed condition has the potential to improve quality of life because it may reduce odour, exudate, pain or result in fewer dressing changes. The clinical experts noted that it is difficult to robustly measure wound improvement. However, validated quality of life tools should capture aspects of wound improvement. The committee considered that improved wound bed condition has an important place in wound care, particularly for some people who have long-term chronic wounds that do not heal within 12 months.

Uncertainties in the reporting of the BWAT score from Bellingeri 2016

4.7 The most robust evidence (a randomised controlled trial by Bellingeri 2016) was at low risk of bias but underpowered based on the statistical analysis plan. It showed a significant reduction in Bates-Jensen wound assessment tool (BWAT) score for Prontosan compared with saline. The external assessment centre noted that it is unclear from the study whether all 13 dimensions of the tool were used. It was not confident that a reported BWAT score of 13 or 14 in this paper can be interpreted as wounds that have healed, or that are approaching healing.

Relevance to the NHS

The evidence from Bellingeri 2016 may be generalisable to NHS practice

4.8 The clinical experts said that they had not used the BWAT score in NHS practice. However, they agreed that it is a comprehensive wound assessment tool. They said most of the factors in the BWAT, including state of wound bed, wound size, sign of infection, pain, exudate and type of dressing, are part of wound assessment tools used in the NHS. However, clinical experts also noted that there are no universally agreed wound assessment tools. The committee concluded that the BWAT is likely to reflect clinical assessments of wounds and may be generalisable to other wound assessment tools used in the NHS.

NHS considerations overview

Prontosan does not add to the appointment time if the soak is applied at the start of the appointment

4.9 The clinical experts told the committee that Prontosan solution is often applied as a soak (for 10 to 15 minutes) for chronic wounds. The experts noted that this can lead to an increase in appointment times in some cases (primarily wound clinics) but that if the tasks are switched around

and the soak is applied at the start of the appointment this should not extend the appointment time. The committee concluded that some education and training may be needed to ensure healthcare professionals know to soak with Prontosan solution at the start of an appointment.

Prontosan is part of a wound care package, so the treatment effect is hard to establish

4.10 The committee noted that Prontosan is part of a wound care package and almost uniformly not used on its own. This means it is difficult to isolate the treatment effect of Prontosan on chronic wounds. The clinical experts stressed the importance of using a locally agreed wound care pathway and explained that treatments are selected using a holistic approach and clinician experience. People with chronic wounds do not necessarily see the same clinician, and use of products and dressings can vary between visits based on what is available. One clinical expert said it would be easier to use one solution consistently rather than decide between multiple solutions (water, saline or Prontosan). Examples of local wound care pathways where Prontosan had been implemented were provided during consultation. The committee concluded that it is hard to isolate the direct effect of Prontosan and recognised the need for an appropriate wound care pathway for chronic wounds.

Cost modelling overview

The cost models are acceptable but any cost modelling using the available evidence is likely to be flawed

4.11 The committee agreed that the clinical and cost case were dependent on each other. Prontosan would result in cost savings even if there was only a small benefit in healing rate or reduction in infection rate. The clinical inputs in the model had some concerns or were at high risk of bias. They were also subject to the same uncertainty as discussed in the clinical evidence section. The committee concluded that more research was needed to establish the clinical and cost benefits of using Prontosan in the NHS. Until then, any cost modelling is likely to be flawed.

Further research

Randomised controlled trials comparing Prontosan with saline or water in the NHS are needed

4.12 The committee concluded that further research is needed to address the uncertainties about the clinical effectiveness of Prontosan compared with saline or water. It recommended that randomised controlled trials should be done in the NHS. These should compare Prontosan with saline or water in different types of chronic wounds. The randomised controlled trial needs to be well designed to detect clinically meaningful results in subgroups (for example, pressure ulcers or venous leg ulcers). The committee agreed that a key outcome should be time to complete wound healing. The number of dressing changes should also be recorded for each wound included in the study. Other important outcomes should include pain and wound odour, measured using patient-reported outcome measures (PROMs).

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technology 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 technology 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 technical analysts (who act as technical leads for the topic), a technical adviser and a project manager.

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Accreditation