**Introduction**

This article describes in detail the composition, mode of action, evidence base and the practical application of a generation of advanced topical treatments containing collagen and oxidised regenerated cellulose, which are designed to convert the non-healing chronic wound environment to a healing state. It is important that clinicians know how and when to use these advanced treatments in order to deliver efficient and effective wound management.

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**What is Promogran?**

Promogran protease modulating matrix is an advanced topical treatment for chronic wounds that has the potential to alter the wound environment in a positive way to promote healing. This can help to improve outcomes for patients with static or hard-to-heal wounds.

Promogran is an absorbent open-pored, sterile, freeze-dried matrix that is composed of 55% collagen and 45% oxidised regenerated cellulose (ORC). These are both natural materials that are readily broken down or reabsorbed when placed in the wound.

When the collagen/ORC matrix comes into contact with fluid/exudate in the wound, it absorbs the liquid to form a soft gel. This allows the dressing to conform to the shape of the wound and come into contact with all areas of the wound. The gel physically binds to and inactivates damaging proteases, both matrix metalloproteases (MMPs) and elastase that are present within the wound. In addition, it binds with naturally occurring growth factors and prevents them from being broken down by damaging proteases. As the matrix slowly breaks down, the growth factors are released back into the wound in an active form, while the damaging proteases remain inactive.

**What is Promogran Prisma?**

Promogran Prisma wound balancing matrix is a version of Promogran that includes silver. This provides protection against bacteria, while allowing healing to progress. Although the theory of combining these materials is very simple, in practice achieving the optimal concentration of silver to avoid adverse affects on cell growth was quite complicated. From laboratory investigations it was found that the that the optimum formulation or combination involved preparing a silver-ORC compound at a 1% concentration.

In addition, Promogran Prisma has an increased amount of collagen and ORC in the dressing compared to Promogran. This increases the overall density of the product and extends the time taken for collagen and ORC to biodegrade in the wound. This is important since when there is an increased bioburden, exudate levels are also elevated.

**How are the products made?**

Both products are formed by preparing medical-grade collagen and fibres of oxidised regenerated cellulose in a liquid suspension. In the case of Promogran Prisma, silver-ORC fibres are added at this stage. The suspension is then frozen and placed under a vacuum. In this frozen form the water in the formulation exists as ice crystals, which sublimes (turns directly from a solid to a gas) under the high vacuum, and is gradually removed from the frozen material. When all of the water has been removed, the remaining collagen/ORC is left as a 3D structure. This dehydration process (known as lyophilisation or freeze-drying) allows for the structural properties of these natural materials to be preserved and is widely used in the pharmaceutical industry to prepare highly stable drug formulations.

The products are manufactured as a 3mm-thick sheet, which is cut into hexagonal pieces. Wounds are generally more circular in shape, but producing a circular-shaped dressing leads to a high level of waste material in the production process. The product was therefore shaped as hexagonal pieces; this provides a repeating pattern, minimising waste and each piece closely resembling a circular shape.

**What is the role of collagen?**

Collagen derives its name from ‘kolla’, the Greek word meaning glue. Although collagen was known to the Romans as early as AD50, its structure was not clearly defined until 1955, and it was not until the 1970s that collagen was discovered to be a family of proteins with at least 28 members.

Today, collagen is recognised as a major structural protein that is present in all animals and is used to support and connect bodily tissues and internal organs. It is one of the most abundant proteins in the human body, making up 25% of the total protein and is a major constituent of skin, bone, tendons, muscles and cartilage.

It is an extremely important protein and has a number of unique physical and biological properties that are essential for function. Collagen has a high tensile strength and has an important role in tissue repair (Box 1). It has been used extensively in a wide range of medical fields, including wound healing, haemostasis, sutures, artificial heart valves and arteries, hernia repair, and soft tissue augmentation. Collagen type 1 is most commonly used and can be isolated from skin (animal hide) or tendon.
What is the role of ORC?
Cellulose is a natural biomaterial found in most vegetation and constitutes about one third of all plant matter, making it the most abundant biomaterial on earth. In its natural form it cannot be digested or degraded by humans and consequently has limited application. However, once it is chemically modified through oxidation the material is readily degraded and absorbed by the body\(^1\). The regenerative process produces fibres of uniform diameter that oxidise in a reproducible manner, creating a material that has consistent physical and chemical characteristics. ORC has been used clinically for over 50 years and is more effective at reducing protease levels than either component alone\(^3,4\). This reduction in protease activity is rapid and sustained, even when the material breaks down.

Chemically, cellulose and ORC are both classified as polysaccharides, sugar molecules linked together to form a polymer; in the case of ORC, the main components are glucose and glucuronic acid. When ORC fibres absorb fluid such as saline solution or wound exudate, they swell and become a gel and break into their basic components (sugars), which can be completely absorbed\(^1,5\).

As the ORC degrades, the glucuronic acid is released, which has the effect of lowering pH; a low pH is thought to help control bacterial growth by inhibiting it\(^5,6\). In addition to its haemostatic and bactericidal properties, in vitro studies have shown that ORC stimulates cell migration and growth\(^7,8\). Studies have also shown its ability to reduce protease levels, specifically human neutrophil elastase and MMPs; scavenges free radicals; and bind excess metal ions\(^9,10\).

Box 1 The role of collagen in tissue repair
- Helps to stop bleeding (haemostatic properties)
- Has a low-inflammatory and low-antigenic response, which does not cause an adverse reaction (even when collagen from different species is used)\(^11,12\)
- Enhances the deposition of new collagen and reduces wound contraction\(^11\)
- Collagen fragments (peptides – formed on degradation of the dressing)\(^11\) can attract cells into the wound area (chemotaxis) and induce cell growth (cell proliferation)\(^11,12\)
- Collagen peptides break down to amino acids, which can be reused by the cells to help build new proteins
- Reduces MMP activity, an effect that helps control the proteolytic environment in the chronic wound\(^13\)

How do the dressings work?
Chronic wounds have been shown to contain elevated levels of inflammatory cytokines, free radicals and proteases, creating a hostile wound environment that is detrimental to healing\(^12,13\). This perpetuates wound chronicity as it causes further tissue damage and degradation of key functional molecules. These include growth factors, which are required to stimulate cell growth and the production of new tissue\(^20,21\). The presence of bacteria exacerbates the problem and amplifies an already hostile environment, increasing the inflammatory response with increased levels of bacterial proteases\(^22,23\) (Figure 1).

It is important to correct this underlying biochemistry to initiate healing. Promogran and Promogran Prisma can be used to modify the wound environment. These products may reduce the harmful factors such as proteases, free radicals and excess metal ions, while simultaneously protecting the positive factors such as matrix proteins and growth factors, leading to an overall increase in new tissue formation and progression towards healing (Box 2)\(^12,20,29,31\).

Effect on bioburden
Collagen/ORC may help to control bacterial growth by inhibiting it\(^5,6\). In addition to its haemostatic and bactericidal properties, in vitro studies have shown that ORC stimulates cell migration and growth\(^7,8\). Studies have also shown its ability to reduce protease levels, specifically human neutrophil elastase and MMPs; scavenges free radicals; and bind excess metal ions\(^9,10\).

Box 2 The role of collagen/ORC in wound healing
- Reduces protease activity, including both MMPs and human neutrophil elastase
- Reduces inflammation (scavenges free radicals and binds metal ions)
- Controls bacterial bioburden
- Protects growth factors from degradation
- Stimulates cell growth and cell infiltration into the wound area

Published studies have shown that collagen/ORC reduces both MMP and serine protease activities, and is particularly effective against MMP-8, MMP-9 and elastase\(^29\). Furthermore, the combination of collagen and ORC is more effective at reducing protease levels than either component alone\(^34\). This reduction in protease activity is rapid and sustained, even when the material breaks down.

In vitro and clinical studies\(^29,31-35\) have shown that the level of inflammatory cytokines and proteases are reduced in the presence of collagen/ORC. Its ability to scavenge free radicals, an end-product of inflammation, and to bind endotoxins and excess metal ions such as iron and zinc, which can induce further inflammation, provides indirect support for its favourable effect on the inflammatory process\(^29\).

Effect on proteases
Many studies have shown that both MMPs and serine proteases are elevated in chronic wounds. In particular, MMP-8 and 9 and human neutrophil elastase, all of which are inflammatory-derived proteases, have been shown to be the most predominant proteases in the chronic wound environment\(^29,32,33\).

Figure 1 Chronic wound environment

<table>
<thead>
<tr>
<th>High levels</th>
<th>Low levels</th>
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<tbody>
<tr>
<td>Proteases</td>
<td>MMPs</td>
</tr>
<tr>
<td>Bioburden/ infection</td>
<td></td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td></td>
</tr>
<tr>
<td>Growth factors</td>
<td>Cell proliferation</td>
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bacterial levels through its ability to lower pH, an effect attributable to the ORC component. The addition of silver-ORC to the formulation has been shown to be non-cytotoxic and may help to reduce the number of pathogens in the wound, irrespective of bacterial bioburden.

What is the evidence base for Promogran/Promogran Prisma?

Collagen/ORC dressings have been evaluated in several randomised controlled clinical trials to measure their performance in diabetic foot ulcers, pressure ulcers and venous leg ulcers. In addition to the published trials, there are many case studies describing the beneficial effects of these dressings on a wide range of wounds.

While these studies demonstrate the clinical effectiveness of Promogran and Promogran Prisma, they do not address the interactive nature of these matrices. However, several investigators have performed clinical research studies to examine the mechanism by which collagen/ORC can modify the wound environment.

For example, Lobmann et al. treated 33 patients with Promogran versus a control dressing for eight days and removed tissue biopsies at three separate time points to measure protease levels. They concluded that the wounds treated with Promogran had shown a greater reduction in wound size compared to the control dressing (16% vs 1.65%). Biochemically, Lobmann et al. found that Promogran-treated wounds showed a reduction in the MMP9:MM2 ratio. Further analysis demonstrated that this reduction in protease levels was not due to an alteration in the production of MMPs but was more likely to be due to the binding of the MMPs to the matrix.

One study has shown that wound fluid levels of MMPs and neutrophil elastase were reduced in wounds treated with...
collagen/ORC dressings and that these wounds subsequently healed within six to 12 weeks\(^{35}\). This result was confirmed in a larger study by Smeets et al, who reported a significant reduction of several key proteases, including gelatinases, elastase and plasmin, when wounds were treated with Promogran compared to a control dressing. This biochemical effect was associated with a reduction in wound size\(^{30}\).

A number of RCTs on Promogran Prisma are ongoing and indicate improved wound healing compared to controls while providing protection from infection\(^{36,46,47}\). Further definitive studies are needed to confirm these initial findings.

### When is Promogran/ Promogran Prisma indicated?

These dressings can be considered for use on wounds that have failed to proceed through an orderly and timely reparative process towards healing\(^{36}\). Lazarus et al defined this as any wound that shows little or no progression over an eight-week period\(^{48}\). Mustoe et al defines a chronic wound as one that is present for longer than 12 weeks and has failed to reach closure\(^{49}\).

### When should you use Promogran?

Promogran can be used for the treatment of exuding wounds including venous leg ulcers, diabetic foot ulcers and pressure ulcers. In practical terms, if a patient presents with a wound that has shown little change in the appearance of the wound bed or edges, and the size has remained the same, Promogran should be considered. The aim of the treatment is to ‘kick start’ healing where the wound appears to have got ‘stuck’.

### When do you use Promogran Prisma?

Promogran Prisma can be used on wounds that show signs of local infection or where a low-grade infection is suspected (see case study below). It may be appropriate to use Promogran Prisma if there has been a history of recurrent local infection, when the dressing can be used prophylactically as a preventative measure.

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### Step-by-step guide to application

**Step 1: Prepare the wound bed**

Before any application of Promogran or Promogran Prisma, the wound bed should be prepared according to local policy. This will usually involve removal of necrotic or sloughy tissue and any previous dressings.

**Note:** If there are signs and symptoms of an infection, this should be treated appropriately and the use of Promogran Prisma considered.

**Step 2: Assess the level of exudate**

The products are supplied pre-packed and packaged in a tray. This can be used to hold saline to pre-wet the dressing if the wound has a low exudate level. Alternatively, a small amount of saline can be added to the surface of the dressing once it has been applied to the wound bed. This helps to initiate the breakdown

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### Promogran Prisma case study

Mr W is an 81-year-old man with type 2 diabetes and a recurrent venous leg ulcer of 11 months’ duration. His main problem has been the failure of the ulcer to progress for approximately six months. Mr W had a previous ulcer in 2002, which achieved complete healing.

Mr W presented with an inactive ulcer to his right lateral malleolus. The ulcer measured 3.5cm\(^2\) with an approximate depth of 0.3cm, and no apparent undermining. The surrounding skin was macerated, erythematous and excoriated with eczema and atrophia blanche. Exudate levels were moderate and there was a slight odour present. This may have been indicative of the presence of bacteria, which if left untreated, may have caused a local or systemic infection. Mr W had previously been treated with a sodium carboxymethylcellulose primary wound dressing (Aquadelle\(^{16}\)) and had also treated the wound himself with Manuka honey. He was complaining of mild, intermittent pain.

The wound was dressed with Promogran Prisma. As a result of presenting symptoms it was felt the use of the silver in the dressing may prevent the development of any local infection. The dressing was prescribed for use twice weekly in combination with modified compression therapy. Mr W had been unable to tolerate high compression bandaging in the past. A thin knitted viscose secondary dressing (NA-Ultra\(^{16}\)) was used with gauze padding. A steroid cream (Eumovate) and white soft paraffin were applied to protect the surrounding skin. Tracings and photographs were taken every 1–2 weeks.

**Outcome**

Two weeks after commencing treatment, the wound bed appeared healthier, with granulation tissue visible at the base. The wound measured 2.5cm\(^2\) in area and depth had decreased to 0.2cm. Two weeks later, the wound appeared to be 100% granulating, with no depth and an area of 1cm\(^2\).

On the last recorded assessment, the wound was unchanged in area, but had a slight depth again of 0.2cm. The wound remained healthy in appearance. Mr W had also reduced the amount of compression during this time, which may have affected healing.

Over the course of six weeks, Mr W has made good progress towards healing with the use of Promogran Prisma combined with compression therapy. He finds the dressing comfortable when in situ and has requested to continue using the dressing. Mr W’s ulcer healed within four weeks of the final evaluation.
of the dressing and its ability to modify the wound environment.

Note: the choice of the secondary dressing is dependent on the level of exudate.

**Step 3: Apply the dressing**

Place the dressing in the wound bed. If the patient has multiple small wounds the dressing can be broken into smaller pieces with a gloved hand.

Note: if there is any depth to the wound the dressing should be layered to fill the wound.

**Step 4: Dressing review**

Based on instructions of use, the dressing should be changed every 72 hours or more frequently if the exudate level is high. If the gel has not biodegraded the dressing should be left in place until the next dressing change, minimising disturbance to the wound. If there is no residue of gel in the wound bed or traces left on the secondary dressing and the wound bed is clean and granulating, the dressing has fully biodegraded. Both products can be used under compression bandaging and do not cause indentation, skin irritation or maceration, even when the dressing is overlapped at the wound edge.

**What factors indicate this is the right dressing choice?**

From personal experience, during the first few dressing changes there should be a change in the colour of the wound bed and a reduction in the amount of sloughy tissue present. Following two weeks of treatment there should be a marked reduction in the level of exudate. Often the first change is that patients report a reduction in the level of pain experienced.

**When should treatment be discontinued?**

There is no need to stop Promogran or Promogran Prisma if the wound is progressing well. However, if the wound is epithelialising and there is no exudate, it may be more appropriate to change to a simple non-adherent dressing.

**When is treatment contraindicated?**

Neither product should be used on patients with full-thickness burn injuries, active vasculitis or a known hypersensitivity to either collagen or ORC. If infection is present or suspected, it should be treated according to local policy. Promogran Prisma can be used with systemic antibiotics to treat infection.

**What are the economic arguments for using this treatment?**

A case for using these products can be made if they can be shown to accelerate healing and reduce the number of dressing changes. This may be supported by evidence from clinical trials. In addition, it is important to consider factors such as reduction in pain because many patients may experience high levels of pain, which can affect all aspects of daily life and may cause poor sleeping patterns.

Furthermore, Phillips et al have reported that many patients with leg ulcers experience negative financial, social and psychological effects, which are resolved once the ulcer is healed.

Often decisions about which dressing to use are based on limited clinical experience. Patients may see a number of practitioners and be prescribed different dressings by each. This may lead to a lack of continuity of care with poor rationale for treatment choice, which may negatively impact on costs. It is therefore important that clinicians understand when and how to use these products appropriately to ensure optimum outcomes for patients.

**Useful links**

For clinical experiences using these products go to: http://woundsinternational.com/article.ph p?issueid=303&contentid=1296&articleid=8836&page=1

For product information go to: www.systagenix.co.uk/our-products/promogran
www.systagenix.co.uk/our-products/promogran-prisma

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**Summary**

Promogran and Promogran Prisma are designed to provide an optimum wound healing environment and to modify the wound biochemistry, by reducing excessive protease activity to promote healing. These dressings can be considered in a wide range of wounds to ‘kick start’ healing.

**To cite this publication**

References