TECHNOLOGY UPDATE:

Expert consensus on a new enzyme alginogel

Flaminal® (Flen Pharma) products are alginate gels containing a novel antimicrobial enzyme system. They are designed to promote wound healing and to restore bacterial balance and their use on a wide range of wound types is supported by scientific and clinical evidence[1–4]. Extensive clinical usage and trialling in Europe and Australasia have provided an evidence base and a list of clinicians with an understanding of the clinical performance of Flaminal products. This expert panel reported that Flaminal products should be classified as 'enzyme alginogels' and identified four key functions — continuous wound debridement; antimicrobial activity; maintenance of a moist wound healing environment; and protection of wound edges and epithelial cells. These enzyme alginogels are compatible with the TIME framework, as demonstrated in the case histories. For example, like honey, they are one of the few materials said to have a number of modes of action[5], however, unlike honey they do not sting when applied to wounds[6]. Furthermore, Flaminal's triple mode of action avoids the need for multiple products, for example, it has the capability to absorb excess exudate while remaining in a gelled state, promote debridement and control bioburden.

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Useful links

Antimicrobial dressings made easy

It is widely appreciated that cellular and molecular imbalances in the wound bed can often delay healing[7]. Models such as the TIME framework — Tissue management, Inflammation and infection control, Moisture balance, Epithelial (edge) advancement — offer a logical and systematic approach to wound bed assessment[8,9].

Table 1 summarises the disturbances in wound bed remodelling associated with each stage of the TIME framework and the relevant treatment approaches.

However, the clinical reality is that clinicians often have to deal with several aspects of the TIME framework at the same time, which requires ongoing assessment and realignments in treatment, often using multiple products.

FLAMINAL

Flaminal® Hydro and Flaminal® Forte (Flen Pharma) are the first items to become available in a new class of wound care products — the enzyme alginogels. They comprise hydrated alginate polymers in a polyethylene-glycol (PEG) matrix embedded with a patented antimicrobial enzymatic complex (GLG — glucose oxidase combined with lactoperoxidase, stabilised by guaiacol[1,10]. These naturally occurring enzymes are found in saliva and milk, and, as such, are important in the innate immune system. They have excellent biocompatibility with very limited, if any, likelihood of allergy (in the six-year life of the product, there has been one suspected allergic contact dermatitis and one irritant reaction).

Working in concert, these two enzymes, lactoperoxidase and glucose oxidase, form free radicals via hydrogen peroxide, which destroys the cell walls of adsorbed bacteria in a manner similar to our innate white cell defences[10]. As this is a selective process, only the absorbed bacteria are destroyed and not the essential regenerating cells of the healing wound.

Evidence

Recent in vitro preclinical studies have demonstrated that low concentrations of this GLG-enzyme system kill antibiotic-resistant bacterial strains without being cytotoxic to fibroblasts and keratinocytes[2,3]. Its mode of action is summarised in [*Fig 1*].

The published clinical data include studies on both acute and chronic wounds, for example, a 70-patient comparative study on partial-thickness hand burns[11], patients with venous leg ulcers[12,1], and, an i*n vivo/in vitro* antimicrobial study on various chronic wounds with supporting cytotoxicity in vitro[2].

In a retrospective study on two groups of 30 patients exhibiting burns, Hoeksema et al[13] reviewed 10 years of clinical experience with Flaminal.

After stratifying burns treated with either Flaminal or with silver sulfadiazine 1% cream according to depth, both superficial (p=0.013) and deep partial-thickness wounds (p=0.04) healed faster with Flaminal treatment — without the requirement for ancillary wound treatments.

Recently, Durante[4] published a report on 23 patients treated with Flaminal for up to 60 days. In this study, a mix of acute and chronic wounds were treated with Flaminal to control exudate and bioburden as part of the standard care protocol. Dressings were changed every 1–4 days according to the manufacturer's instructions and/or clinical need.

TIME component	Wound bed disturbance	Approach
TIME	Tissue necrosis Barrier to further healing	Removal of necrosis (debridement) via: - Sharp debridement (surgical/bedside) - Wet-to-dry dressings - Hydrogels - Enzymes - Biosurgery - Negative pressure treatment.
TIME	Inflammation and infection Imbalance between microorganisms and host resistance, leading to delayed healing	Control of infectious agents: - Topical antibacterial treatment - Wet dressings with topical antiseptics - Iodophors - Tea tree oil-based products - Polyhexamethylene biguanide (PHMB) - Silver dressings - Sugar and honey.
TIME	Moisture imbalance Increased exudate resulting in increasingly wet wound and border maceration	Need for absorption of excessive fluid: - Alginates - Foam dressings - Hydrofibers - Super-absorbent filler dressings. Need to protect wound borders
TIME	Non-migrating wound edge	Surgical reconstruction Biologic wound dressings Skin-replacing biologic dressings

Table 1 Summary of the TIME model of wound care and the appropriate treatment approaches for each stage

Page Points

1. *Flaminal gel is designed for the management of exuding acute and chronic wounds, and bioburden control*
2. *A panel of international experts has recommended that it be designated an 'Enzyme alginogel' to reflect its composition*
3. *The panel has also reviewed all available evidence and has prioritised the use of Flaminal gels to four key functions:*
   - *continuous wound debridement*
   - *antimicrobial activity*
   - *maintenance of a moist wound healing environment*
   - *protection of wound edges and epithelial cells.*

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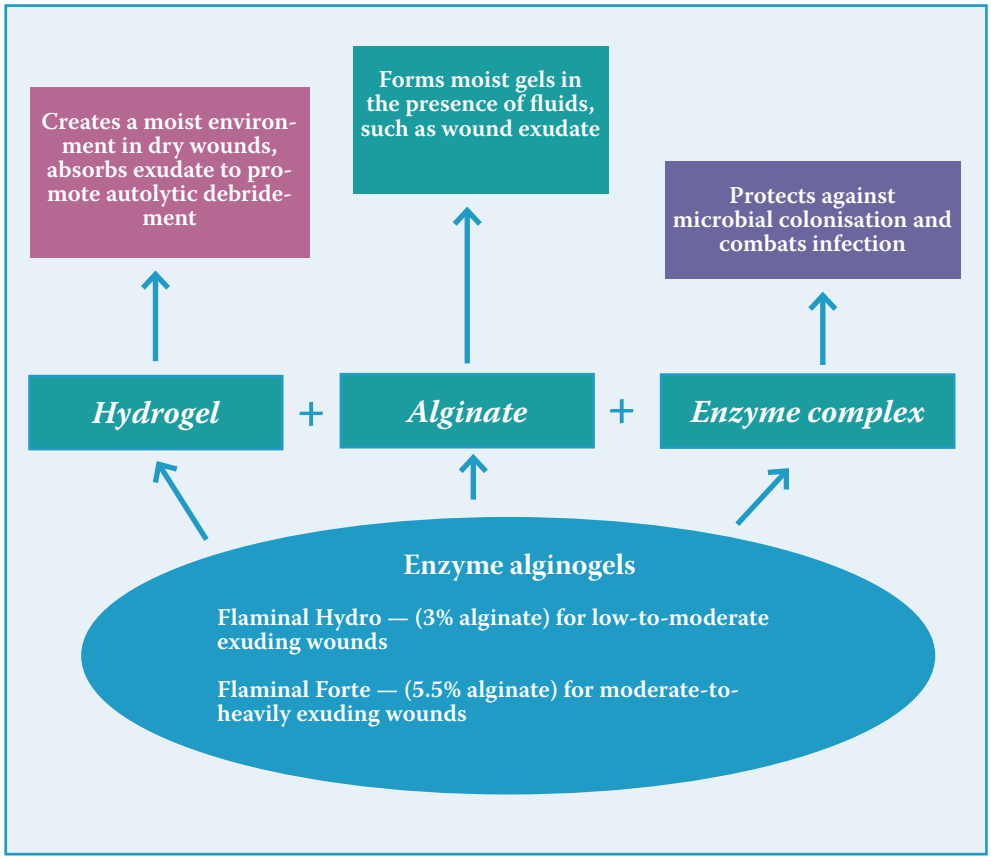

Figure 1: The components and mechanism of action of Flaminal (White, 2006).

For wounds exhibiting moderate-to-high exudate levels, foams were used; for low-to-medium exuding wounds, dry dressings were used. Wound volume and surface area were measured at the start of the study and routinely afterwards — the mean volume on inclusion was $2.8 \pm 5.6 cm^3$ and the mean area $2.6 \pm 3.8 cm^2$.

Wound pain, surface area and volume, exudate levels, and wound tissues were assessed regularly until healing, or until 60 days had elapsed. Results showed that in all wounds there was a significant decrease in dimensions ($p \leq 0.001$). This included chronic wounds refractory to treatment with other modalities (treatment of over 12 weeks' duration). In each group of patients wound pain (as assessed using a visual analogue scale [VAS]) decreased over time.

THE EXPERT PANEL

The expert panel used their clinical experience of Flaminal products, in conjunction with the published evidence, to consider where enzyme alginogels might be positioned according the to the 'T', 'I' and 'M' elements of the TIME framework ('E' components involve biological dressings or surgery and are not appropriate).

The panellists brought the following case evidence to the discussion.

CASE STUDY EVIDENCE

Australian experience

A 91-year-old female patient presented with a three-week-old full-thickness burn to the foot [*Fig 2*]. She received daily Flaminal therapy following her request to continue with her daily commitments prior to a femoro-popliteal bypass and a skin graft. The extent of healing after three weeks of daily dressing changes is shown in [*Fig 3*].

Further evidence is presented via the experience of an 88-year-old female patient with dementia who presented with a full-thickness burn to the knee [*Figs 4-7*].

The use of Flaminal not only avoided the need for hospitalisation, with the associated risk of pressure ulceration, but also facilitated rapid healing, as demonstrated in [*Fig 7*]. The efficacy of Flaminal in older patients with burns, a group with high comorbidity rates

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5. White RJ. Natural approaches to wound management: a focus on honey and honey-based dressings. *Wounds UK* 2005; 1(3 Suppl): S1–60.

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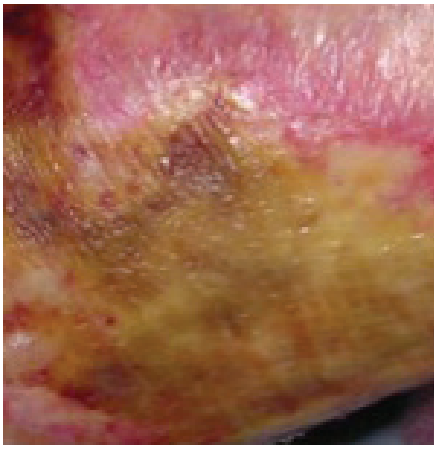


Figure 2. Full-thickness burn to the foot.

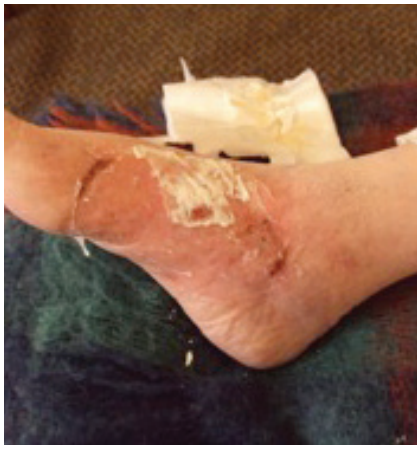
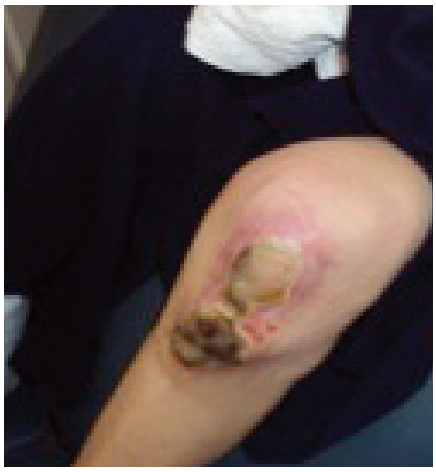
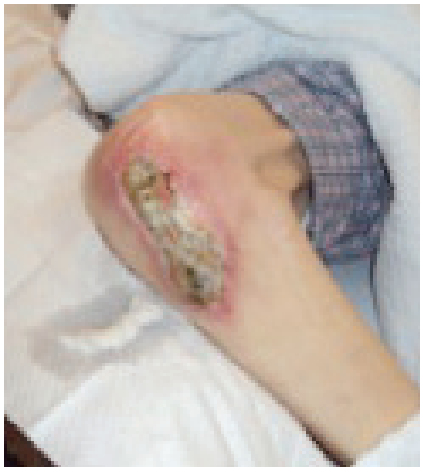
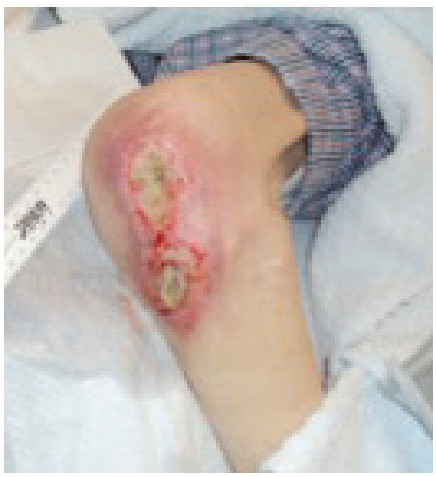


Figure 3. Healing extent of burn after three weeks' treatment with Flaminal.







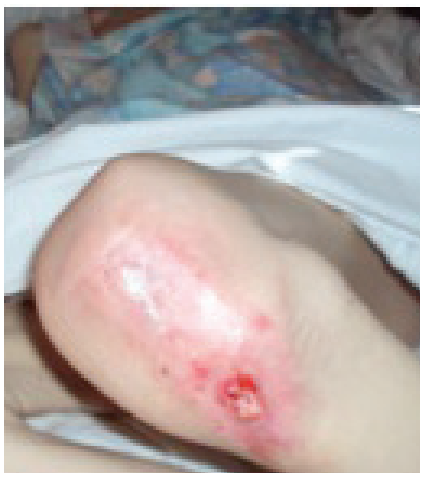


Figure 4. Full-thickness burn to the patient's knee before treatment (above).

Figure 5. The wound after two weeks of daily dressings (above).

Figure 6. The wound after three weeks of daily dressings.

Figure 7. The wound at 13 weeks.

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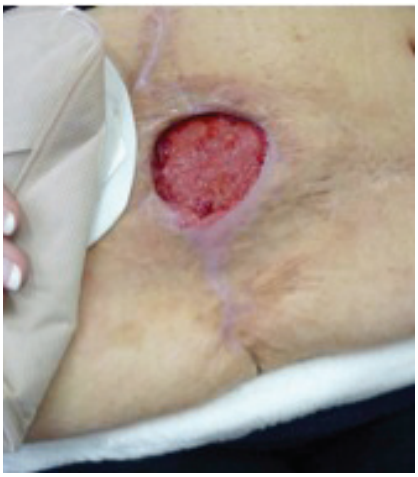

Figure 8: Recurrent parastomal hernia before treatment.

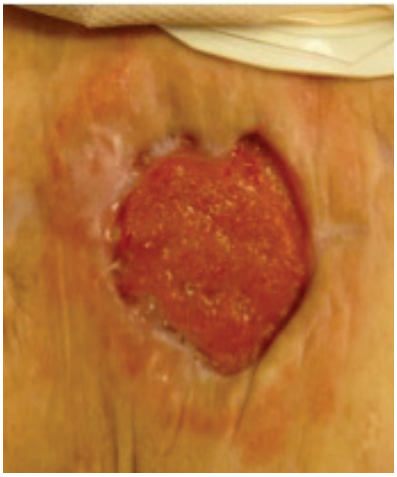

Figure 9. The same wound following two months of treatment with Flaminal.

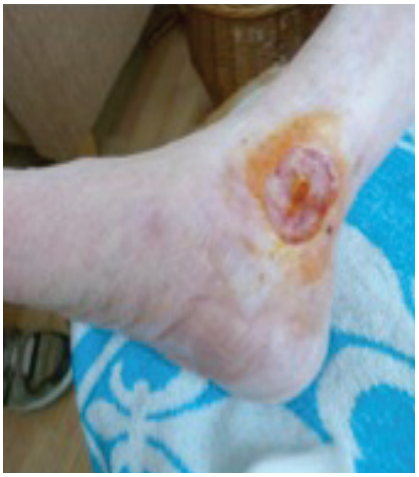

Figure 10: A venous leg ulcer before Flaminal treatment.

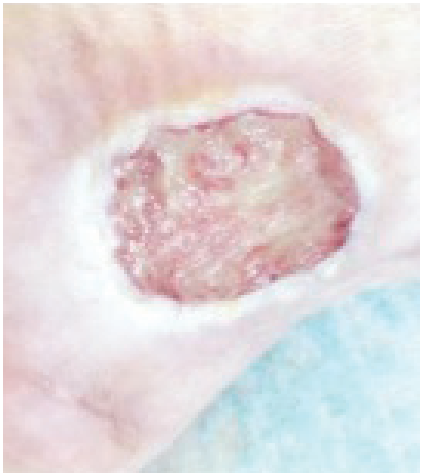

Figure 11: The same wound after three weeks of Flaminal treatment.

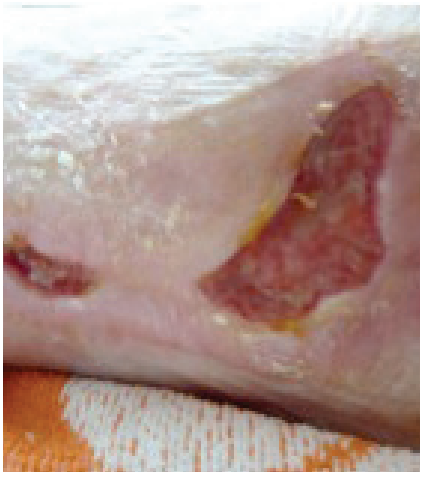

Figure 12: After six months, the wound had reduced in size from 12cm² to 8.9cm².

who are often malnourished, is clear — it helps to manage fluid levels and bioburden as well as aiding debridement. Furthermore, the author's experience has shown that when patients who have experie nced pain with a cadexomer iodine try Flaminal, they are more than satisfied with both the comfort and efficacy of the product.

Dutch experience

A patient who had undergone bowel resection and colostomy with unsuccessful abdominal reconstruction presented with recurrent parastomal hernia, which was exuding, infected and measured 25cm² [*Fig 8*]. An alginate dressing (Kalostat®, ConvaTec) and a Hydrofiber (Aquacel®, ConvaTec), as well as negative pressure wound therapy (NPWT), were tried over a period of 8–9 months, without effect. Flaminal products were then used, and after two months of daily treatment the wound reduced by 1cm² [*Fig 9*]. The patient has since chosen to continue with Flaminal Hydro.

In another case, a 92-year-old female patient with venous leg ulcers of over 45 years' duration commenced Flaminal Forte therapy at the end of April 2011. Previous treatments included a variety of hydrogels with compression therapy (Actico®, Activa). After three weeks, the wound tissue appeared healthier even without sharp debridement, although there was no change in size [*Fig 10-11*].

These results suggest that Flaminal

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may have promoted granulation tissue formation. After continued use of Flaminal three times a week for six months,the wound reduced in size from 12cm^2 to 8.9cm^2 [*Fig 12*].

Czech experience

A 60-year-old man presenting with an infected venous leg ulcer of three months duration was treated with Flaminal. The wound exhibited necrotic margins and high exudate levels with an expanding area of wound pain. Swab tests were positive for Pseudomonas aeruginosa and Escherichia coli. This man was previously under the care of a GP who had opted for local antibiotic ointments and compression bandages. The new strategy involved daily dressing changes (with effective compression), using Flaminal without the concurrent administration of oral antibiotics. [*Fig 13-16*] demonstrate therapeutic antimicrobial activity through bioburden reduction. The Flaminal also managed the associated exudate and was easy to use.

Of clinical significance was the finding that after one week the wound was granulating and clear of slough. After one month, swab tests for infection were

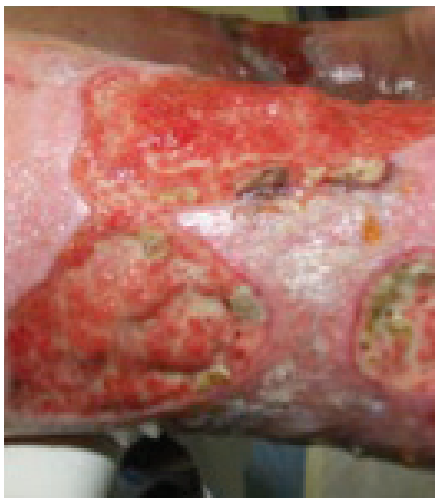

Figure 13: Venous leg ulcer in a 60-year-old man (above).

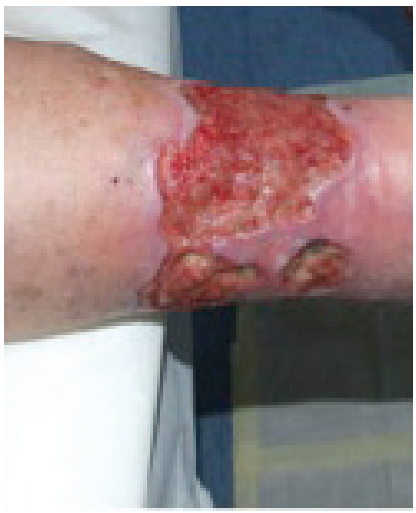

Figure 14: The same wound area shown after one week's treatment (above).

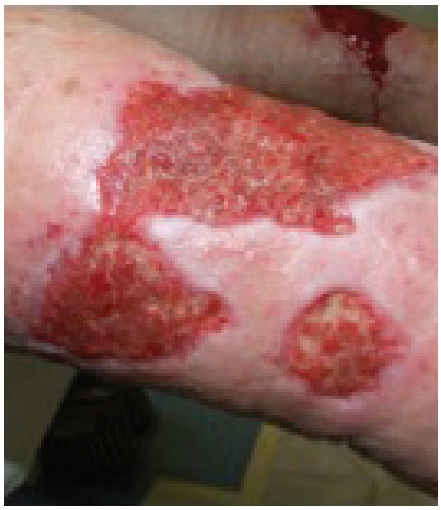

Figure 15: The wound after one month's treatment.

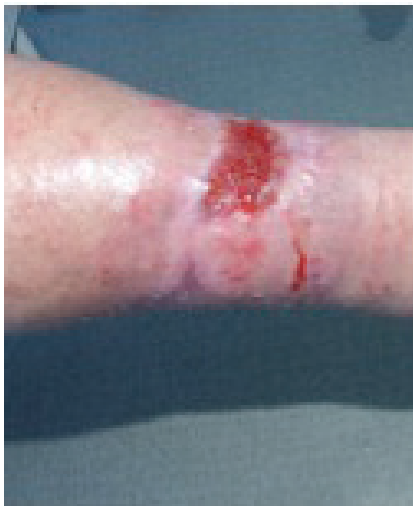

Figure 16: The wound after five months' treatment.

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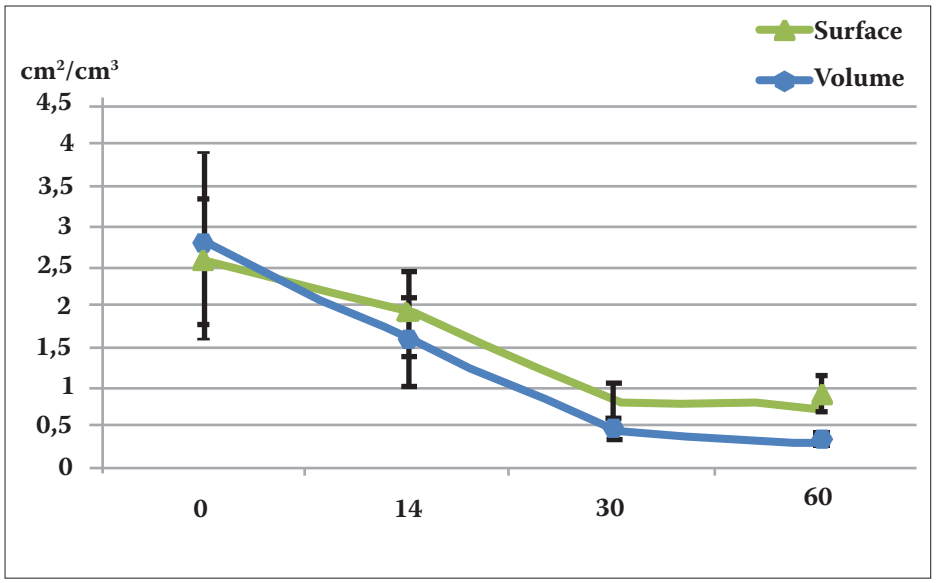

Figure 17: Mean (+SEM) change in wound size and volume over time.

negative, wound pain and exudate were reduced and healing was evident.

While antimicrobial activity is generally not the primary objective of clinical observations/consultations (this is reserved instead for research studies), experience in over 20 cases has so far revealed that Flaminal can have a positive effect on infected ulcers.

Italian experience

This was a single-centre, open-label case series investigating the efficacy of Flaminal in 23 patients with acute and chronic wounds of diverse aetiology (*Table 2*). Flaminal was applied in accordance with the manufacturer's instructions and wounds were covered with secondary dressings. A scheduled treatment protocol was applied and patients were assessed at 14, 30 and 60 days. As shown in [*Fig 17*], this treatment facilitated a clear reduction in wound size and volume over time.

It is also noteworthy that in four of the pressure ulcer cases, healing was evident after just six days of treatment. Further analysis of healing progression is shown in [*Fig 18*], which illustrates a quantitative overview of the presence of epithelium, granulation, fibrin and necrosis for each wound type prior to treatment (week 0) and after two, four and eight weeks.

The wounds began responding within two weeks of treatment, with higher proportions of fibrin, granulation and epithelium visible, as well as a lack of necrosis. [*Fig 19*] summarises how pain levels (visual analogue scale [VAS] evaluation) fluctuated before, during and after dressing change at the associated time points, suggesting a trend for a dampening of patient perceived pain over time — this effect may have contributed to the improved healing seen over time [*Fig 17*], or could have resulted from the healing and reduction in size.

These quantifiable outcomes are supplemented by feedback from the care givers: 'Flaminal is very easy to use and provides the option to incorporate a second dressing of choice [the study incorporated non-adherent dressings and gauze but foams were most often used] — its presence beneath other dressings has not presented any issues.

It demonstrates very good efficacy in wounds with predominant Gram-positive organisms and compliance with Flaminal schedules has also been noted after one year in some cases'[4].

Classification and reimbursement — a French perspective

The French perspective focused on the current reimbursement structure in France. Two classes of hydrogels are recognised at present — physical and chemical — and Flaminal falls into the later. Alginates are also a recognised category in the reimbursement of dressings in France — they vary according to carbohydrate

References

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	Frequency (%)	Acute (n)	Chronic (n)	Median duration (range), days
Pressure ulcer	9 (39.1)	0	9	335 (128–7,128)
Diabetic ulcer	7 (30.4)	3	4	246 (22–1,593)
Traumatic wounds	3 (13.0)	2	1	77 (0–397)
Arterial ulcer	1 (4.3)	0	1	1,195 1
Other	3 (13.0)	3	0	0 (0–731)
Total	23 (100)			

Table 2 – Patient demographics in a single-centre, single-arm, open-label case series investigating the efficacy of enzyme alginogels.

structure in terms of fluid uptake. The 'enzyme alginogel' classification suggested for Flaminal currently does not fit any existing French category.

The requirement to demonstrate reference to a traditional product has already been fulfilled, in as far as Flaminal has been compared with Intrasite® Gel (Smith & Nephew) [1], which was found to be effective at reducing wound volume and surface area at seven days.

However, larger well-designed randomised clinical trials are needed with outcome measures including healing rates and wound area regression after four or more weeks of treatment[14,15].

MODES OF ACTION

Based on its composition and modes of action, Flaminal is positioned as an enzyme alginogel. Enzyme alginogels should be positioned thus in clinical application:

- Exudate management: there is a standard British Pharmacopaeia test, which has been accepted as a European Standard (European Community, 2011)[16]. Multiple samples of Flaminal Forte and Hydro have been subjected to this test in isolation and found to absorb 31.7% and 16.3% of their weight respectively. According to the Standard, this puts them in classes 4 and 2
- Bioburden management
- Autolytic debridement.

The concentration of alginate was selected carefully so that light to moderate exudate was managed by Flaminal Hydro and heavier levels by the Forte product — bioburden management is facilitated via the neutrophil-like peroxidase contained in the gel[17] (Van Den Plas et al, 2006).

Autolytic debridement could be demonstrated by the effective moisture balance achieved, which is vital to promote optimum healing[18].

There was a consensus among the panel brought together for this document that there was limited evidence of autolytic debridement published in clinical reports, despite the positive results achieved without the need for sharp surgical debridement, and that further investigation is needed in this area.

Additionally, as clinicians frequently have to deal with multiple aspects of the TIME framework simultaneously, having a product with a triple mode of action could be cost-effective. Other benefits include its ease of use, particularly in small and hard-to-reach wounds, such as diabetic foot ulcers.

Compared with alternative dressings, such as aliginates in sheet form, Flaminal is highly conformable.

Furthermore, its antimicrobial effect is not accompanied by any cytotoxicity (contrary to experience with other antimicrobials, such as silver). As the antimicrobial effect is not that of a commonplace topical antibiotic, resistance is highly unlikely.

The panel stated that further analysis of the effect of Flaminal on wound bacterial colonisation and the formation of biofilms would be appropriate.

Page Points

1. *Based on its composition and modes of action, Flaminal is positioned as an enzyme alginogel.*
2. *Flaminal is highly conformable and its antimicrobial effect is not accompanied by any cytotoxicity, in contrast to other antimicrobials, such as silver.*

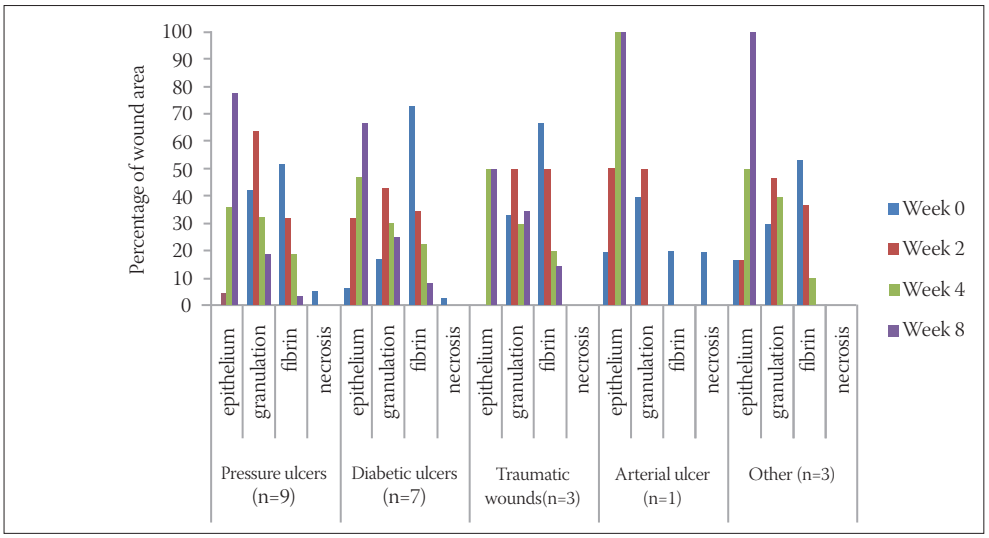

Figure 18: The proportion of wound area covered by epithelium, granulation, fibrin and necrosis during the study for each wound type.

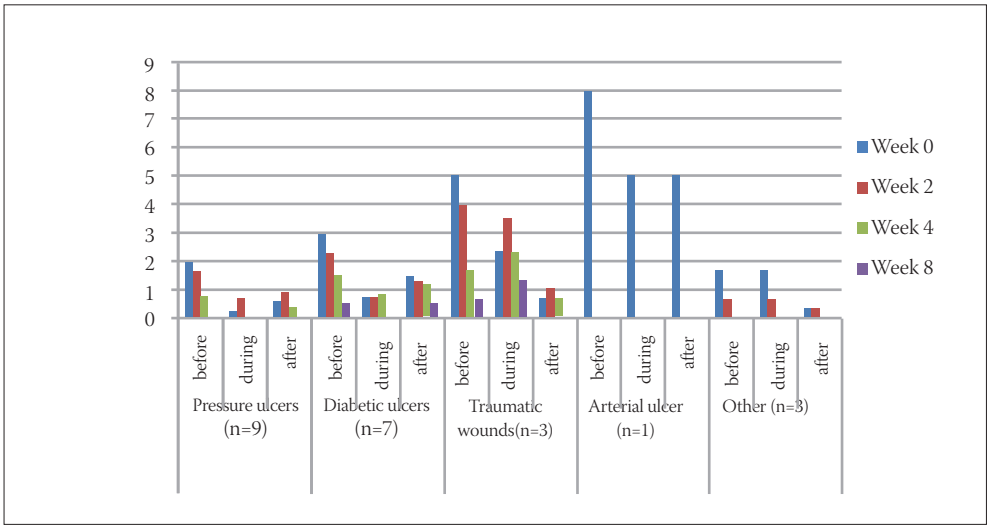

Figure 19: Evolution of pain, as measured by VAS pain score, before, during and after application of the enzyme alginogel (adapted from Durante, 2012).

CONCLUSION

While the composition of a dressing is important for classification, its mechanism of action should possibly be a greater influence on dressing selection. Flaminal, with its triple mode of action [*Fig 1*], is unique and so should not be regarded as either hydrogel, alginate or antimicrobial, but rather as a synthesis of the three. Similarly, its unique enzyme component affords an antimicrobial function with negligible risk of selecting for resistance. The general consensus of this meeting of wound care clinicians is that there is a place for this new class of dressing in care frameworks, but that it also presents a need for the following:

- Larger scale randomised clinical trials to demonstrate efficacy of the main performance characteristics listed above
- Performance versus current comparative competitors (some are listed in *Table 1* for the 'T', 'I' and 'M' aspects of the TIME framework);
- In vivo proof of the unique antimicrobial action of the enzyme component.

While the clinical evidence to date is definitely promising, these further studies are needed to confirm that Flaminal can avoid the unnecessary requirement for multiple products, presenting a real cost saving and supporting applications for reimbursement from healthcare authorities worldwide.

ACKNOWLEDGEMENT

Richard White is a consultant to Flen Pharma.

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