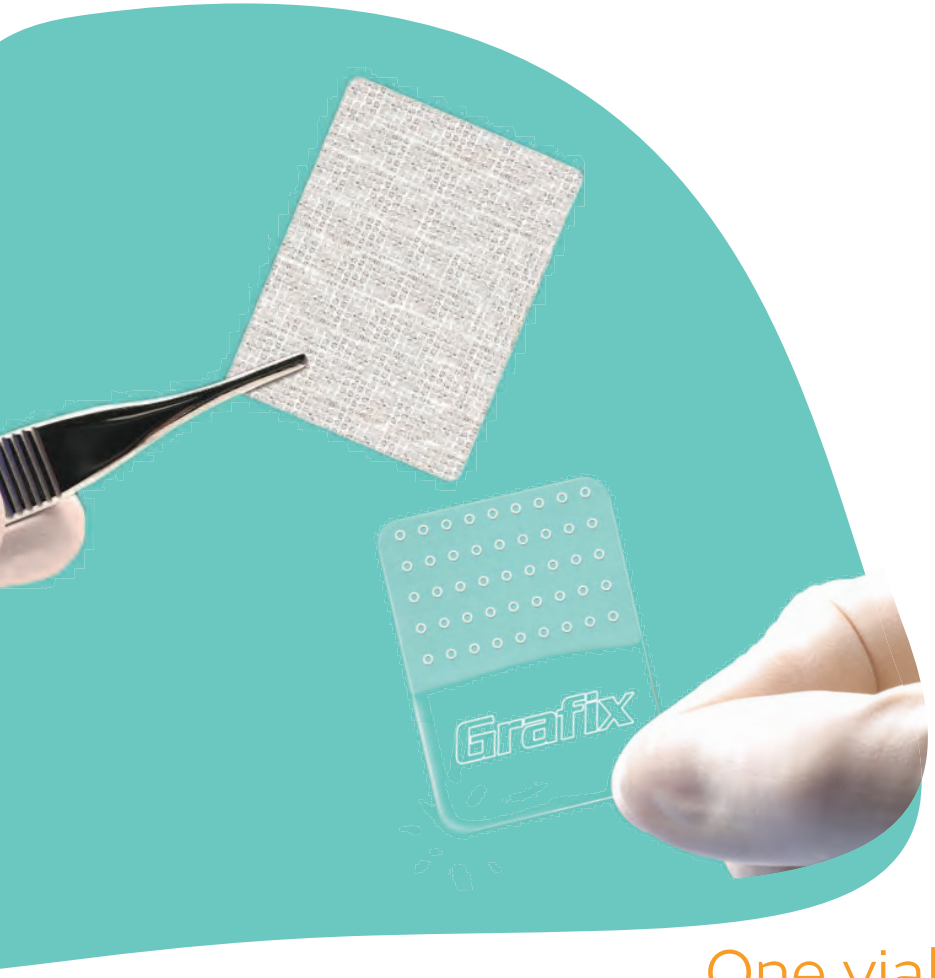


One viable tissue
✚ Two preservation methods
✚ Three natural components

Placental membranes for wound management composed of native viable cells, growth factors, and extracellular matrix

Smith+Nephew

GrafixPL◊

Lyopreserved Placental Membrane

Grafix◊

Cryopreserved Placental Membrane

Did you know?

Wounds can be devastating to your patients' lives and hospital outcomes. Major disability, poor quality of life, and reduced productivity contribute to the growing financial burden.[1-3] When healing stalls, so do the lives of your patients.

Diabetic foot ulcers

1.5
million U.S. patients affected each year[4]

85%
of lower limb amputations in patients with diabetes are preceded by ulcerations[5-7]

40%
recurrence rate within 1 year[8]

Venous leg ulcers

1
million U.S. patients affected each year[4]

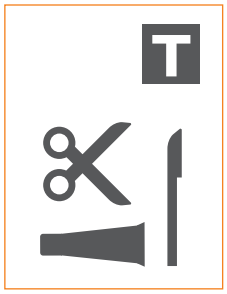
66%
fail to heal with standard of care (SOC) in 12 weeks[9-11]

70%
recurrence rate within 3 months[12]

Wound duration is an independent **risk factor** for infection, hospitalization and amputation, contributing to significant patient morbidity and cost of care

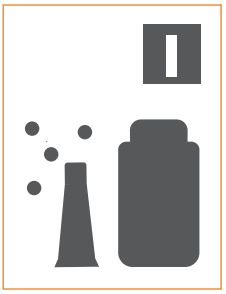
What if there was a better solution for your patient?

An evidence-based approach for wound preparation to advance chronic wounds toward healing[13-15]



Tissue is non-viable or deficient

Debridement[13-16]

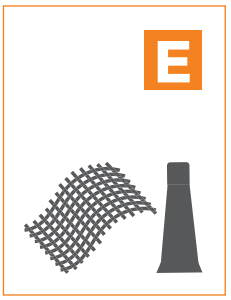


Infection, inflammation, and biofilm

Bioburden management[13-15]

Moisture imbalance

Exudate management[13-15]



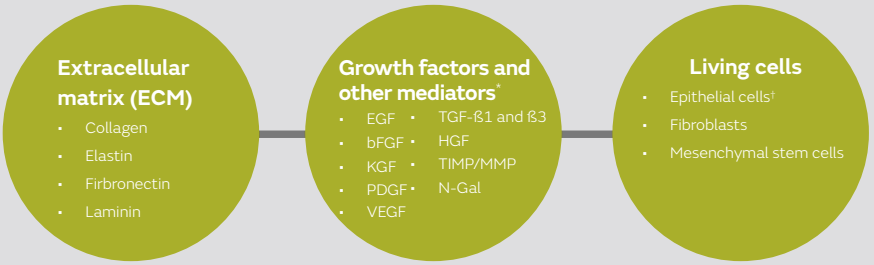
Epithelial edge advancement

Promote epithelialization[13-15]

Placental membranes may promote re-epithelialization of chronic wounds[17]

- Advanced cryopreservation and lyopreservation methods preserve the native properties and components of fresh placental membranes
- Other tissue preserving methods may alter or destroy the components and/or properties of fresh placental membranes[18-21]

Placental membrane components



Aseptic cryopreservation[22]	Preserved	Preserved	Preserved
Aseptic lyopreservation[22]	Preserved	Preserved	Preserved
Traditional dehydration / radiation	Altered	Altered	Altered

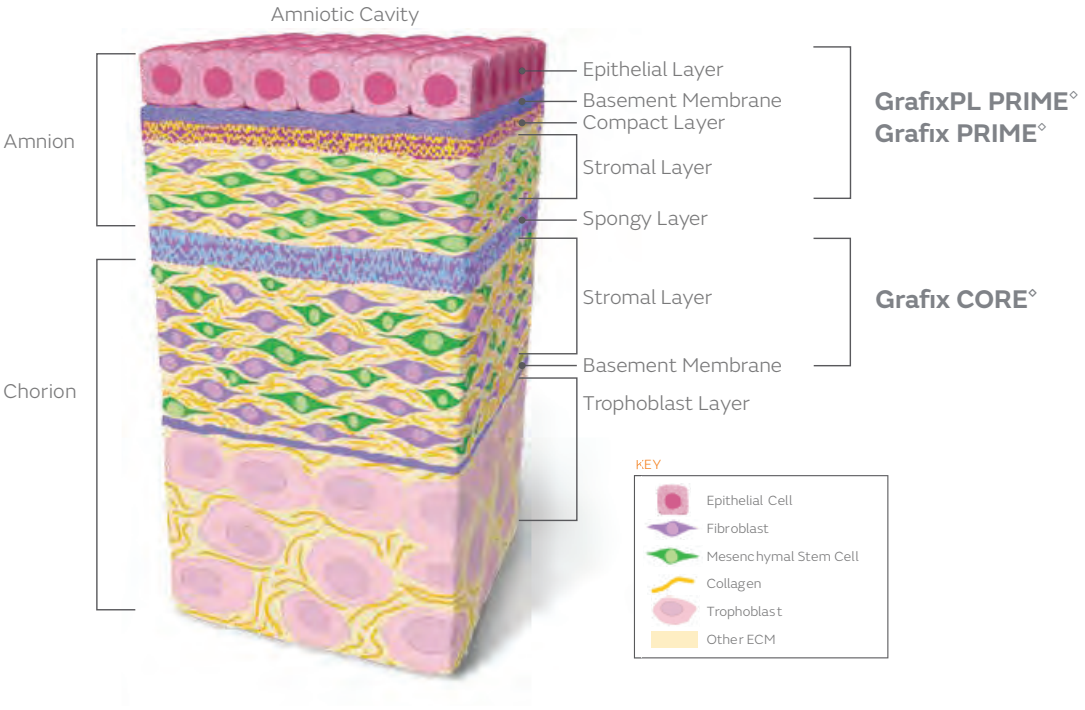
*List not inclusive of all growth factors.
†Present in amnion only.

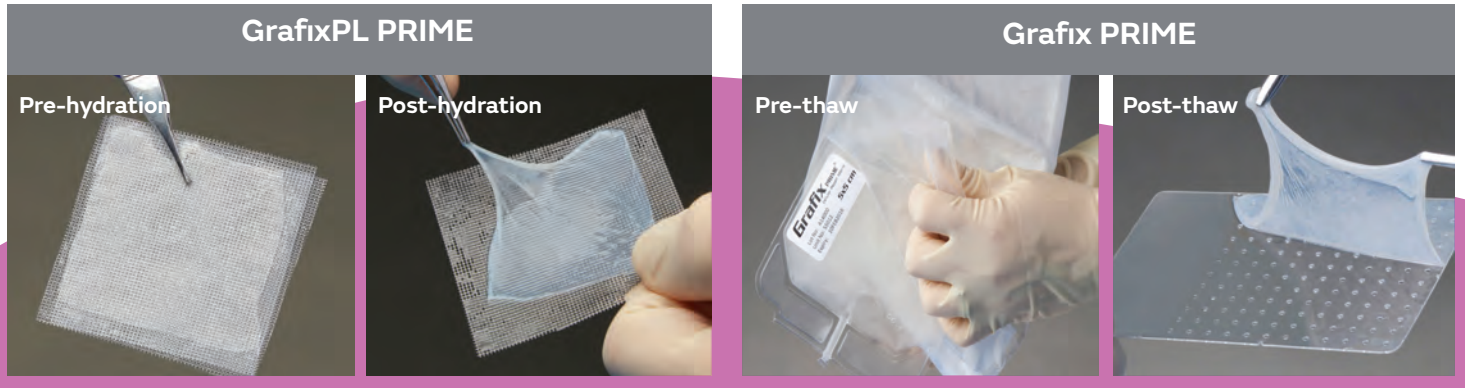
GrafixPL◇ + Grafix◇

About

- Lyopreserved or cryopreserved placental membranes derived from the amnion or chorion placental membranes
  - GrafixPL is lyopreserved and stored at room temperature
  - Grafix is cyropreserved and stored at -75°C to -85°C
- Trophoblast layer and maternal components removed to prevent an immune response
- Can be used as a wound cover or surgical wrap

Cross-section of the placental membranes





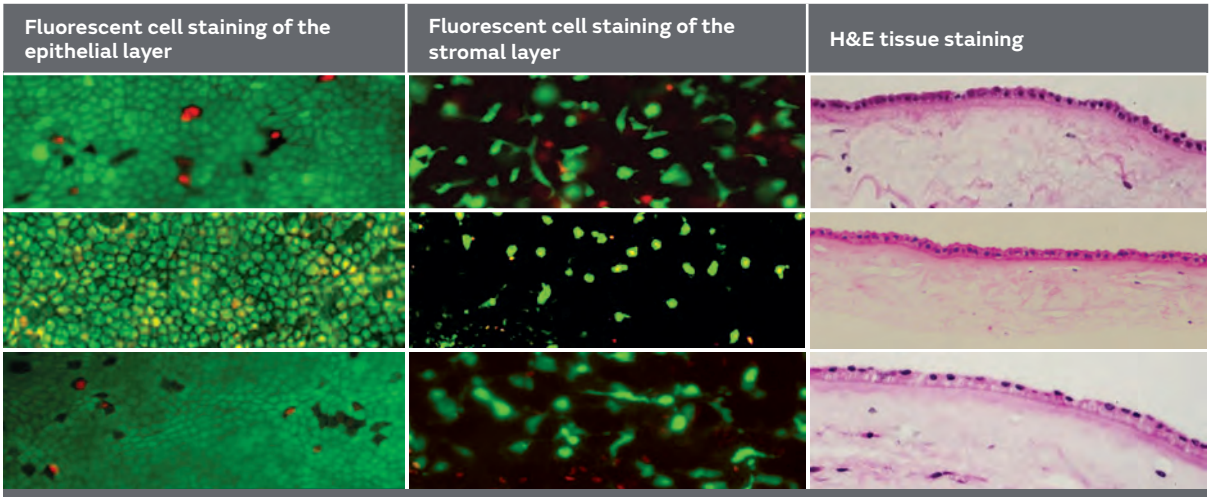
Hydrated GrafixPL PRIME and thawed Grafix PRIME are equivalent[22]

Engineered by nature + optimally preserved + available on demand

Many placental membrane products are available, but most have only growth factors and an extracellular matrix. All three native components of placental membranes, including viable cells, are preserved in GrafixPL® and Grafix®.

Endogenous cells remain viable[22]

3D matrix remains intact[22]



LIVE and DEAD cell staining

The presence of viable cells in GrafixPL and Grafix was independently confirmed by researchers at Rutgers University, Montana State University and the University of Texas Southwestern.[23-24]

Native growth factors are retained[22]

	Fresh amnion	GrafixPL PRIME	Grafix PRIME
IL-10	■	■	■
IL-1RA	■	■	■
PDGF-BB	■	■	■
bFGF	■	■	■
SDF-1α	■	■	■
Angiopoietin-1	■	■	■

Quality evidence + Results driven

Grafix◇ delivered statistically significant improvements over standard wound care for closing diabetic foot ulcers[25]

Study overview[25]

- Prospective, 20-center, randomized, single-blinded, controlled trial*
- Third party blinded image verification

Results[25]

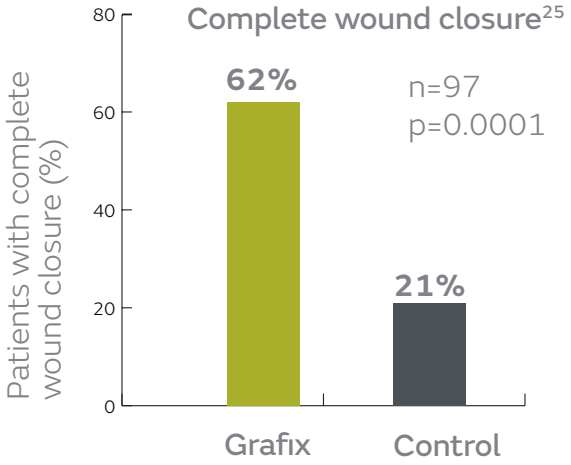
Significantly higher complete closure rate

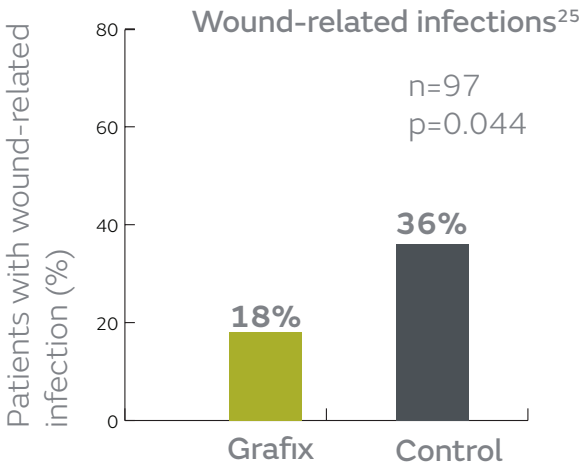
(62% vs. 21%)

- Faster median time to complete closure (**42 days vs. 70 days**)
- Decreased number of treatments (6 vs. 12)*
- Fewer wound complications (44% vs. 66%)
- Fewer wound-related infections (18% vs. 36%)
- **65% complete closure** in the open-label crossover phase for patients who previously failed with standard treatment in the control group[26]
- Fewer infection-related hospitalizations (6% vs. 15%)

Consideration[25]

- At the pre-specified interim analysis, study enrollment was terminated at the recommendation of the blinded review committee due to the superiority of Grafix versus the control





*Trial had three phases: 1) a blinded phase of treatment with weekly Grafix (n=50) vs treatment with standard of care alone (n=47) with a primary endpoint of 100% re-epithelialization by week 12; 2) a follow-up phase with visits every 4 weeks for an additional 12 weeks; and 3) an open-label phase where patients in the control arm failing to close after 12 weeks were given the opportunity to receive Grafix for 12 weeks.

Faster wound closure
✚ Lower costs[25,27*]

$14,813
lower cost of care for Grafix®-treated patients (n=50) compared to control (n=47, standard of care alone)

$13,828
lower cost of care for closed wounds (n=41) compared to non-closed wounds (n=56)

The lower costs for Grafix-treated patients were driven by faster wound closure, fewer wound complications, and fewer hospitalizations

Low bias
✚ More confidence[28]

Assessment overview

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. NICE evaluated the quality of data for dermal substitute studies that included cure rates at 12 weeks vs standard care in diabetic foot ulcers.

Results

Grafix had the **highest overall effect (z-score)** and was the only study rated as **high quality** with no serious risk of bias

Product	z-score[29]	p-value[29]	NICE quality of evidence rating[30]
Grafix[25]	z=3.55	p=0.0004	High quality with low risk of bias
Dermagraft[31-33]	z=3.13	p=0.002	Moderate quality with serious risk of bias
EpiFix[34]	z=2.13	p=0.03	Low quality with very serious risk of bias
Apligraf[35]	z=2.10	p=0.04	Very low quality with serious risk of bias

*Comparing estimated healthcare costs associated with Grafix versus standard of care alone in the RCT reported by Lavery et al. The cost of care was calculated based on treatments, medications, clinical procedures, and wound complications.

Results in a large, retrospective, WoundExpert analysis of Grafix◇ in DFUs mirror RCT closure rates[36]

Study overview[36]

- Retrospective, 58-center analysis of Grafix in the management of DFUs with Net Health's WoundExpert electronic health record (EHR) database
- Population: All patients who received Grafix in the management of DFUs over a 4-year period were evaluated* (360 patients, 441 wounds)

Patient demographics and wound characteristics	
Multiple wounds† in 4-year period	Approx. 90%
>6 wounds† in 4-year period	Approx. 50%
Wound size (mean)	5.1 cm^2
Wound duration prior to treatment (mean)	102.4 days
Complex wounds with exposed bone, tendon, or joint capsule	14.7%

Results[36,‡]

Complete wound closure (end of treatment)

59.4%

Number of grafts to close (mean)

5.2

Time to wound closure (mean)

57.7 days

Safety outcomes:
Amputations

3%

Related infections

2%

Comparison between EHR real world study and randomized, controlled trial		
Study type	Retrospective, multicenter[36]	Prospective, multicenter RCT[25]
Wounds	350	97 (50 Grafix, 47 Control)
Complex wounds	Allowed	Excluded
Complete wound closure at end of treatment	**59.4%**	**62.0%**

*Exclusion criteria: Wounds missing baseline/follow-up measurements or receiving other skin substitute treatment concurrent with Grafix.

†DFUs and wounds of other etiologies.

‡350 wounds out of the 441 wounds evaluated were analyzed for closure and closure-related outcomes. Wounds ≤ 0.25 cm^2 were not included in the closure analysis. 0.25 cm^2 was chosen as a minimum size for closure analysis since in previous publications of WoundExpert database studies, wounds ≤0.25 cm^2 were considered closed.[37-39]

Overwhelming success in the management of chronic complex DFUs[40]

Study overview[40]

- Prospective, multicenter, open-label, single-arm trial of Grafix® in the management of DFUs with exposed bone and/or tendon
- 31 patients enrolled, 27 patients completed*

Wound characteristics	
Wound duration prior to study (mean)	7.5 months
Wound size (mean)	14.6 cm^2
Prior advanced wound therapy	67.7%

Results[40]

Complete granulation at 16 weeks:

96.3%

Mean 6.8 graft applications in 6.8 weeks to achieve 100% granulation

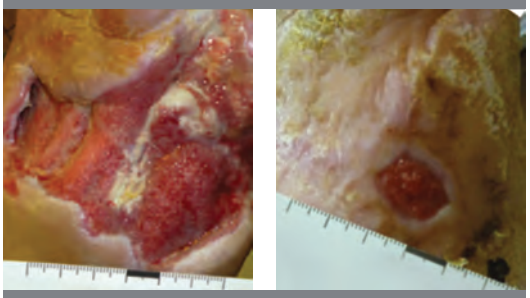
Complete wound closure at 16 weeks:

59.3%

Mean 9.0 graft applications in 9.1 weeks to achieve complete wound closure

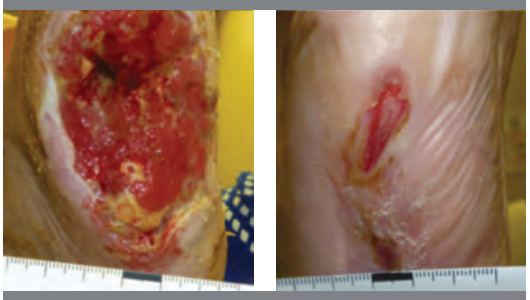
100% Granulation

Case example 1



Week 0 wound area: 70 cm^2 | Week 16 wound area: 0.8 cm^2

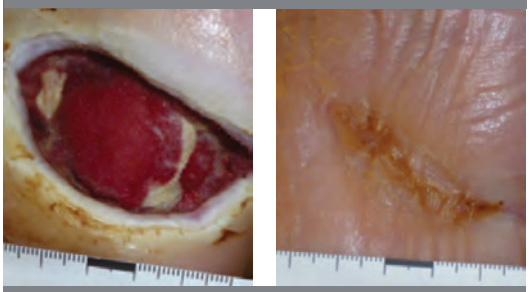
Case example 2



Week 0 wound area: 47.2 cm^2 | Week 16 wound area: 1.2 cm^2

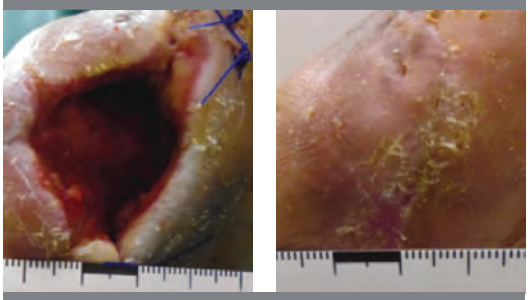
100% Re-epithelialization

Case example 3



Week 0 wound area: 17.4 cm^2 | Week 12 wound closure

Case example 4



Week 0 wound area: 10.8 cm^2 | Week 10 wound closure

*Two patients withdrew for non-compliance and two for surgical intervention.

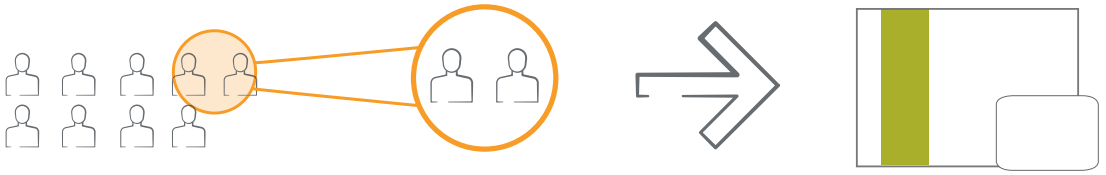
This series of studies is provided for informational and educational purposes only. These cases may not represent typical outcomes. Every procedure and each patient undergoing wound care treatment represents unique sets of circumstances and, therefore, results may vary. Smith & Nephew does not provide medical advice. The information presented is not, and is not intended to serve as, medical advice. It is the responsibility of the treating physician to determine and utilize the appropriate products and techniques according to their own clinical judgment for each of their patients.

Right product + Right time

Grafix◇ helped improve closure of chronic refractory venous leg ulcers[41]

Study overview[41]

- Prospective longitudinal crossover study of Grafix in the management of refractory chronic VLUs
  - Single-center, open-label, single-arm where each patient served as their own control



81 Patients entered 12 week standard therapy phase*

21 patients with 30 VLUs failed to heal with 12 weeks of standard therapy

They crossed over to the 12 week Grafix treatment phase†

Results[41]

VLUs that failed to close with 12 weeks of standard therapy made **significantly greater progress** toward closure when **Grafix** was added to the treatment

Complete wound closure of chronic refractory VLUs:

53%

Mean 7.2 graft applications in

10.9 weeks

12 week follow-up phase

no recurrence

Outcomes of standard therapy phase vs Grafix treatment phase in 21 crossover patients

	Standard therapy phase	Grafix treatment phase	p-value
Baseline wound size (mean)	17.1 cm^2	12.2 cm^2	
Complete wound closure	0%	53%	<0.001
Wound area reduction (mean)	29%	79%	<0.001

*Standard therapy phase: Patients were treated for 12 weeks with SOC (included multi-layer compression).

†Inclusion criteria for the Grafix treatment phase included: 1) failed to heal in standard therapy phase; 2) venous insufficiency confirmed by duplex ultrasound; 3) no infection, ischemia, or immunosuppression; and 4) radiofrequency ablation of the great saphenous vein for patients with evidence of superficial venous insufficiency. Radiofrequency ablation of the ipsilateral great saphenous vein was performed in 14 of the 21 patients at 4 weeks (mean) prior to entering the study.

Chronic wound closure outcomes with GrafixPL◇ suggest clinical equivalency with Grafix◇[42]

Study overview[42]

- Retrospective, open-label, 5-center study on GrafixPL PRIME in the management of chronic wounds*
  - Wounds included DFUs (n=41), VLUs (n=19), surgical wounds (n=10), & other wounds (n=28)†

Patient demographics and wound characteristics	
Patients	78
Wounds	98
Wound size (mean)	13.3 cm^2
Wound duration prior to treatment (mean)	8.7 months

Results[42]

Complete wound closure[42]

59.2%

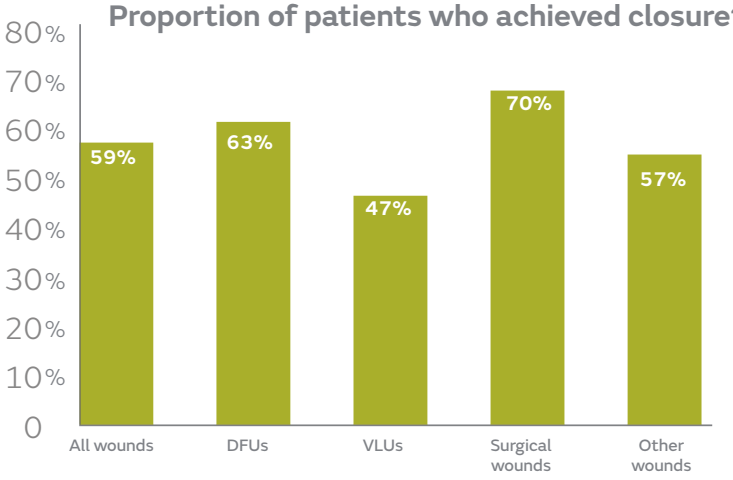
Median 6 graft applications in

63 days

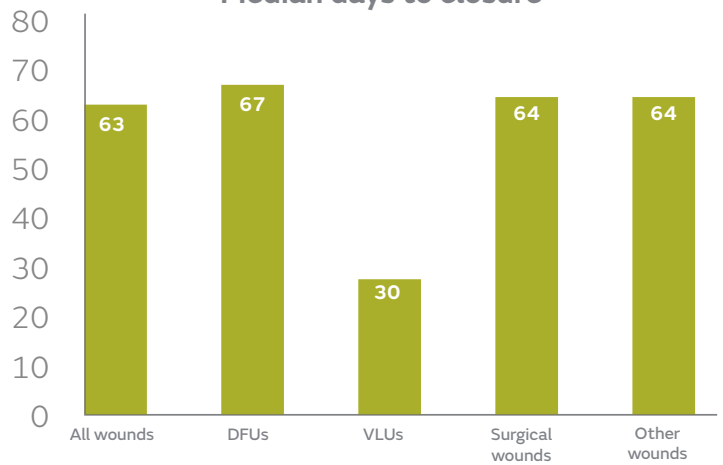
to closure

GrafixPL closure rates similar to those previously reported for Grafix

Proportion of patients who achieved closure[42]



Median days to closure[24,42]



*Defined as wounds with no progression toward closure with 4 weeks of SOC or wounds in patients with significant comorbidities that put them at high risk for nonclosure.

†Other wounds include pressure ulcers, arterial wounds, chronic wounds, open hematomas, gangrenous wounds, radiation necrosis wounds, lymphedema wounds, ischemic wounds, & necrotizing fasciitis.

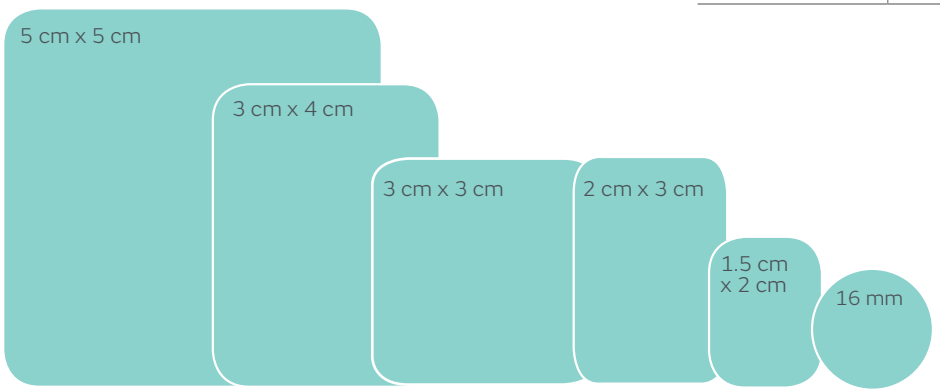
GrafixPL◇ and Grafix◇ are placental membranes composed of native living cells, growth factors, and an intact extracellular matrix

- Designed for application directly to wounds and compromised surgical sites
- Flexible, conforming covers that may be applied over bone, tendon, and other structures
- GrafixPL and Grafix are available in multiple sizes, helping you reduce waste and cost

Placental tissue source	Product description	Part #
Lyopreserved amniotic membrane	GrafixPL PRIME 16 mm Disc (2 cm^2)	PS13016
	GrafixPL PRIME 1.5 cm x 2 cm (3 cm^2)	PS13015
	GrafixPL PRIME 2 cm x 3 cm (6 cm^2)	PS13023
	GrafixPL PRIME 3 cm x 3 cm (9 cm^2)	PS13033
	GrafixPL PRIME 3 cm x 4 cm (12 cm^2)	PS13034
	GrafixPL PRIME 5 cm x 5 cm (25 cm^2)	PS13055

Placental tissue source	Product description	Part #
Cryopreserved amniotic membrane	Grafix PRIME 16 mm Disc (2 cm^2)	PS60013
	Grafix PRIME 1.5 cm x 2 cm (3 cm^2)	PS11015
	Grafix PRIME 2 cm x 3 cm (6 cm^2)	PS11023
	Grafix PRIME 3 cm x 4 cm (12 cm^2)	PS11034
	Grafix PRIME 5 cm x 5 cm (25 cm^2)	PS11055
Cryopreserved chorionic membrane	Grafix CORE 3 cm x 4 cm (12 cm^2)	PS12034
	Grafix CORE 5 cm x 5 cm (25 cm^2)	PS12055

Actual sizes shown



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