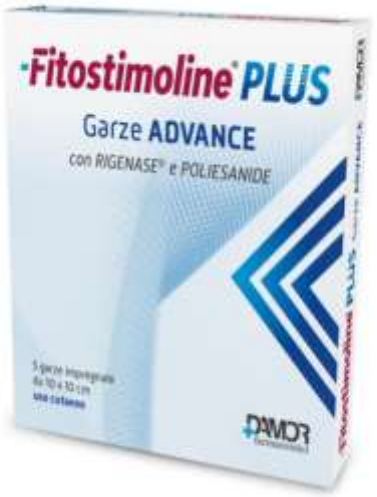
RAPID HTA REPORT		
N° della richiesta	**Data della richiesta**	**Richiedente**
302	18-10-2023	UOC DERMATOLOGIA, SIENA
Tipo di report		
Nuovo report		X
Aggiornamento di un report precedente		
Se aggiornamento, indicare il motivo:		

Dati generali della tecnologia			
Nome commerciale			
FITOSTIMOLINE PLUS GARZE ADVANCE			
Nome generico			
Garza ialuronata impregnata di Regenerase			
Nome fabbricante			
DAMOR Farmaceutici			
Nome fornitore			
Farmaceutici Damor SpA			
RDM	**REF**		
2115989	076701		
Tipo	**Marchio CE (data)**	**Classe di rischio**	**Approvazione FDA**
1	6.2.2020 MED-003868-00	IIb	No
CND			
M04049: MEDICAZIONI PER FERITE, PIAGHE E ULCERE - ALTRE			
Problema clinico e razionale della richiesta			
Medicazione di ferite di varia natura e ulcere			
Indicazioni d'uso			
Medicazione di ferite di varia natura e ulcere			
Paziente target			
Pazienti affetti da a) ulcere croniche da decubito di origine venosa o di origine vascolare mista; b) deiscenza chirurgica; c) ulcere infiammatorie; d) ustioni di primo grado; e) esiti di ustioni di secondo grado; f) lesioni post-traumatiche; g) abrasioni.			
Principali competitor			
Si sottolinea che il richiedente propone un utilizzo del DM in 2 fasi consecutive: nella prima fase vengono utilizzate medicazioni avanzate con proprietà antisettiche e successivamente la garze ialuronate			

Dettagli tecnologici
Descrizione
Fitostimoline Plus garze è un dispositivo medico per uso dermatologico costituito da garze monodose, in PET, delle dimensioni di 10x10 cm, impregnate con crema idrodispersibile contenente Rigenase® e Poliesanide, confezionate singolarmente in buste saldate di carta/alluminio/PE. Il prodotto, nel suo confezionamento finale, subisce un processo di sterilizzazione terminale ai raggi γ. Il dispositivo medico Fitostimoline® Plus garze Advance applicato sul derma leso forma una barriera protettiva contro l'ambiente esterno contribuendo al controllo del microambiente della ferita e creando pertanto condizioni favorevoli per una rapida e corretta azione riepitelizzante sulla cute. Il prodotto è quindi indicato per il trattamento di lesioni di diversa eziologia. Il particolare supporto in triplo strato PET consente la gestione di essudati di entità moderata/intensa. Rigenase® è uno specifico estratto di grano. La presenza di Poliesanide riduce il rischio di contaminazione batterica.
Elementi di innovazione
Nessuno in particolare

Evidenze cliniche ed economiche
Studi clinici
Sono tre i principali studi a supporto di questo DM [1-3]. Lo studio di Ricci et al [1], da un lato, è stato pubblicato su una rivista italiana non censita da PubMed, e d'altro lato ha incluso solo 20 pazienti in sperimentazione single-arm, cioè condotta in assenza di un gruppo di controllo. L'analisi verso un gruppo di controllo è stata surrogata da un confronto "dopo vs prima" per ogni paziente confrontato con se stesso. Lo studio di Romano et al. [2] è pre-clinico in vitro e non ha quindi arruolato alcun paziente. Riporta i principali parametri misurati in vitro nella fase di sviluppo farmacologico del DM. Lo studio di Russo et al. [3] è quello più valido, ma ha comunque arruolato soltanto 30 pazienti trattati con Fitostimoline per 6 settimane.
Sperimentazioni cliniche in corso
La banca dati clinicaltrials.gov alla data del 6 Novembre 2023 ha riportato un solo studio in corso in pazienti con fissura anale; non disponibile alcun risultato.
Linee guida
-nessuna
Analisi di costo-efficacia
-nessuna
Report HTA
-nessuno
Benefici attesi
-non quantificati/non quantificabili

Prezzo e costo terapia per paziente

Prodotto (Fabbricante)	Prezzo unitario (euro)	Costo terapia per paziente (euro)	Fabbisogno annuale (N. pezzi)
FITOSTIMOLINE PLUS GARZE ADVANCE (DAMOR)	29.60 € in confezione di 5 garze	Dipende dalla durata della terapia con questo DM; lo	circa 450 garze

Prezzo e costo terapia per paziente			
	(corrispondenti a circa 6 € per garza)	studio di Russo et al (3) che ha usato una durata di 6 settimane.DM	

Prezzo e costo terapia per paziente con le alternative terapeutiche già in uso		
Prodotto (Fabbricante)	**Prezzo unitario (euro)**	**Costo terapia per paziente (euro)**
Il richiedente propone un uso in add-on, perchè un'alternativa terapeutica attiva non è identificabile.		

Impatto economico ed organizzativo
Circa 3000 € annui limitatamente alla struttura richiedente

Informazioni di rimborsabilità			
Diagnosi principale (codice ICD9-CM)	**Intervento (Codice ICD9-CM)**	**Codice DRG**	**Tariffa (euro)**
Svariate, essendo molteplici le condizioni cliniche candidate alla terapia con questo DM	Non identificabile		

Valutazione di innovatività (secondo Delibera regionale N° 737/2022, link e N° 1244/2022 link)	
Dispositivo innovativo (S/N)	N
Se sì, indicare quali Criteri 1, 2 e 3 risultano soddisfatti:	

Dati riassuntivi		
Numero della richiesta	**Data della richiesta**	**Richiedente**
302	18-10-2023	Dermatologia AOUS
Tecnologia		
Dispositivo da usare come medicazione		
Conclusioni		
La richiesta di Fitostimoline PLUS ADVANCE si configura sostanzialmente come un uso off-label del DM dal momento che la posologia proposta nei due studi clinici disponibili prevede una terapia per 6 settimane (differente quindi dalla posologia di durata variabile che il richiedente intende usare). In linea di principio, ciò non rappresenta un motivo assoluto che impedisce una raccomandazione positiva. Tuttavia ciò pone il problema per cui un'eventuale terapia di lunga durata (che comunque non sembra corrispondere alle intenzioni del richiedente) comprenderebbe inevitabilmente un periodo di somministrazione dopo la dimissione del paziente, in cui l'onere economico dell'acquisto ricade sul paziente. Un'eventuale approvazione potrebbe trovare la motivazione del modesto impatto economico che questo DM determinerebbe. Tuttavia, il quadro di impiego del DM appare mal definito e pure diverso dagli studi clinici che sostengono il DM stesso. In conclusione, dato che le evidenze sono scarse e si riferiscono comunque ad un uso di Fitostimoline per 6 settimane, il CO esprime parere sfavorevole considerando insufficienti gli elementi eventualmente a favore del DM. In questa decisione, gioca un ruolo di rilievo il prezzo unitario di Fitostimoline PLUS, che appare notevolmente più elevato rispetto a quello adi altre garze medicate.		
Data di redazione del report		

Dati riassuntivi
14 Novembre 2023
Andrea Messori
Farmacista referente
Donata Iozzi

BIBLIOGRAFIA

1. Ricci E, Pittarello M. Valutazione clinica dell'efficacia e della tollerabilità di un nuovo presidio a base di Rigenase® e poliesanide nel trattamento di lesioni cutanee croniche **Italian Journal of Wound Care**, 2022, № 3, https://doi.org/10.4081/ijwc.2022.92

2. Romano E, Campagnuolo C, Palladino R, Schiavo G, Maglione B, Luceri C, Mennini N. Technical Evaluation of a New Medical Device Based on Rigenase in the Treatment of Chronic Skin Lesions. B**ioengineering** (Basel). 2023 Aug 29;10(9):1022. doi: 10.3390/bioengineering10091022. PMID: 37760124; PMCID: PMC10526047.

3. Russo R, Carrizzo A, Barbato A, Rasile BR, Pentangelo P, Ceccaroni A, Marra C, Alfano C, Losco L. Clinical Evaluation of the Efficacy and Tolerability of Rigenase® and Polyhexanide (Fitostimoline® Plus) vs. Hyaluronic Acid and Silver Sulfadiazine (Connettivina® Bio Plus) for the Treatment of Acute Skin Wounds: A Randomized Trial. **J Clin Med.** 2022 Apr 29;11(9):2518. doi: 10.3390/jcm11092518. PMID: 35566643; PMCID: PMC9105357.

APPENDICE: ABSTRACT DELLE REFERENZE SOPRA CITATE

-Studio di Ricci et al.

In questo articolo si discute il caso controllo di una medicazione composta da Rigenase© (stimolina di origina vegetale) addizionata di poliesanide, su un nuovo supporto in PET in triplo strato nel trattamento di lesioni cutanee croniche dell'arto inferiore. Scopo dello studio è la valutazione in termini di riparazione e controllo del bioburden Batterico. Sono stati arruolati **20 pazienti** con un periodo di run in di 6 settimane con terapia secondo i gold standard; a seguire un analogo periodo di trattamento con la medicazione in studio. I punti in esame sono stati l'evoluzione dell'area, misurata con un sistema basato su intelligenza artificiale come primario. End point secondari: livello di infezione/colonizzazione, WBP e dolore, tutti raccolti mediante scale validate. I dati raccolti inerentemente all'area hanno dimostrato una differenza statisticamente significativa (p<0.0001). differenze significative si sono evidenziate anche in termini di segni di infezione (p<;0.001), WBP score (p<;0.001) e dolore con NRS (p<;0.0001). Non si sono riscontrati eventi avversi od effetti collaterali. Gli autori concludono che la medicazione dimostra una elevata capacità di stimolare la ripresa dei fenomeni riparativi in lesioni con scarsa tendenza spontanea alla riparazione.

-Studio di Romano et al.:

Chronic wound is characterized by slow healing time, persistence, and abnormal healing progress. Therefore, serious complications can lead at worst to the tissue removal. In this scenario, there is an urgent need for an ideal dressing capable of high absorbency, moisture retention and antimicrobial properties. Herein we investigate the technical properties of a novel advanced non-woven triple layer gauze imbibed with a cream containing Rigenase, an aqueous extract of *Triticum vulgare* used for the treatment of skin injuries. To assess the applicability of this system we analyzed the dressing properties by wettability, dehydration, absorbency, Water Vapor Transmission Rate (WVTR), lateral diffusion and microbiological tests. The dressing showed an exudate absorption up to 50%. It created a most environment allowing a proper gaseous exchange as attested by the WVTR and a controlled dehydration rate. The results candidate the new dressing as an ideal medical device for the treatment of the chronic wound repairing process. It acts as a mechanical barrier providing a good management of the bacterial load and proper absorption of abundant wound exudate. Finally, its vertical transmission minimizes horizontal diffusion and side effects on perilesional skin as maceration and bacterial infection.

-Studio di Russo et al.

Objectives: Compare the efficacy and tolerability of Connettivina® Bio Plus (Group A)
gauze and cream, and Fitostimoline® Plus (Group B) gauze and cream for the treatment of acute superficial skin lesions. Design: Single-center, parallel, randomized trial. A block randomization method was used. Setting: University of Salerno—AOU San Giovanni di Dio e Ruggi d'Aragona.
Participants: **Sixty patients** were enrolled. All patients fulfilled the study requirements. Intervention: One application of the study drugs every 24 h, and **a six-week observation period.** Main outcome measures: Efficacy and tolerability of the study drugs.
Results: In total, 60 patients **(Group A, n = 30; Group B, n = 30)** were randomized; mean age was 58.5 ± 15.8 years. All patients were included in in the outcome analysis. Total wound healing was achieved in 17 patients undergoing treatment with Connettivina® Bio Plus and 28 patients undergoing treatment with Fitostimoline® Plus. The greater effectiveness of the latter was significant (p = 0.00104). In Group B, a significantly greater degree of effectiveness was observed in reducing the fibrin in the wound bed (p = 0.04746). Complications or unexpected events were not observed. Conclusions: Both Connettivina® Bio Plus and Fitostimoline® Plus are secure and effective for treating acute superficial skin lesions. Fitostimoline® Plus was more effective than Connettivina® Bio Plus in wound healing of acute superficial skin lesions, especially if fibrin had been observed in the wound bed.

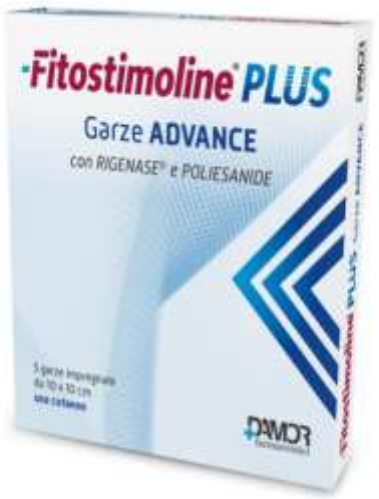
Copia del documento può essere scaricata dal sito http://www.regione.toscana.it/-/prodotti-hta.

Redazione del report a cura del Centro Operativo, Decreto regionale n.17610 del 7 Settembre 2022.

Per ulteriori informazioni scrivere alla mail centro.operativo.htart@regione.toscana.it

A seguire la scheda tradotta automaticamente in Inglese come risulta dal software DeepL (http://www.deepl.com/translator)

RAPID HTA REPORT		
Request No.	**Date of request**	**Applicant**
302	18-10-2023	UOC DERMATOLOGY, SIENA
Type of report		
New report		X
Updating a previous report		
If updating, please state the reason:		

General technology data			
Trade name			
PHYTOSTIMOLINE PLUS ADVANCE GAUZE			
Generic name			
Hyaluronated gauze impregnated with Regenerase			
Manufacturer name			
DAMOR Pharmaceuticals			
Supplier name			
Farmaceutici Damor SpA			
RDM	**REF**		
2115989	076701		
Type	**CE marking (date)**	**Risk class**	**FDA approval**
1	6.2.2020 MED-003868-00	IIb	No
CND			
M04049: DRESSINGS FOR WOUNDS, SORES AND ULCERS - OTHER			
Clinical problem and rationale for the request			
Dressing of various types of wounds and ulcers			
Indications for use			
Dressing of various types of wounds and ulcers			
Target patient			
Patients with a) chronic decubitus ulcers of venous or mixed vascular origin; b) surgical dehiscence; c) inflammatory ulcers; d) first degree burns; e) second degree burns; f) post-traumatic injuries; g) abrasions.			

General technology data
Main competitors
It is emphasised that the applicant proposes to use DM in 2 consecutive phases: in the first phase, advanced dressings with antiseptic properties are used, followed by hyaluronate gauze

Technological details
Description
Fitostimoline Plus gauze is a medical device for dermatological use consisting of single-dose, PET gauze pads, 10x10 cm in size, impregnated with water-dispersible cream containing Rigenase® and Polyhexanide, individually packed in sealed paper/aluminium/PE bags. The product, in its final packaging, undergoes a terminal γ-ray sterilisation process. The medical device Fitostimoline® Plus Advance gauze applied to the injured skin forms a protective barrier against the external environment contributing to the control of the wound microenvironment and thus creating favourable conditions for a rapid and correct re-epithelialising action on the skin. The product is therefore indicated for the treatment of wounds of different aetiologies. The special triple PET layer support allows the management of moderate/intensive exudates. Rigenase® is a specific wheat extract. The presence of polyhexanide reduces the risk of bacterial contamination.
Elements of Innovation
None in particular

Clinical and economic evidence
Clinical studies
There are three main studies supporting this DM [1-3]. The study by Ricci et al [1], on the one hand, was published in an Italian journal not listed in PubMed and, on the other hand, only included 20 patients in a single-arm trial, i.e. conducted in the absence of a control group. The analysis towards a control group was surrogated by an 'after vs. before' comparison for each patient compared with himself. The study by Romano et al. [2] is pre-clinical in vitro and therefore did not enrol any patients. It reports the main parameters measured in vitro in the pharmacological development phase of DM. The study by Russo et al. [3] is the most valid one, but it still only enrolled 30 patients treated with Phytostimulines for 6 weeks.
Ongoing clinical trials
The clinicaltrials.gov database as of 6 November 2023 reported only one ongoing study in patients with anal fissure; no results available.
Guidelines
-no
Cost-effectiveness analysis
-no
HTA Report
-none
Expected benefits

Clinical and economic evidence
-unquantified/unquantifiable

Price and cost of therapy per patient			
Product (Manufacturer)	**Unit price (euro)**	**Therapy cost per patient (euro)**	**Annual requirements (No. pieces)**
PHYTOSTIMOLINE PLUS ADVANCE GAUZE (DAMOR)	29.60 € in a pack of 5 gauze (corresponding to approximately 6 € per gauze)	It depends on the duration of therapy with this DM; the study by Russo et al (3) who used a duration of 6 weeks.DM	about 450 gauze

Price and cost of therapy per patient with existing treatment alternatives		
Product (Manufacturer)	**Unit price (euro)**	**Therapy cost per patient (euro)**
The applicant proposes an add-on use, because an active therapeutic alternative cannot be identified.		

Economic and organisational impact
Approximately €3,000 per year limited to the applicant structure

Reimbursability information			
Main diagnosis (ICD9-CM code)	**Intervention (ICD9-CM Code)**	**DRG code**	**Tariff (euro)**
A variety of clinical conditions are candidates for therapy with this DM	Unidentifiable		

Assessment of innovativeness (according to Regional Resolution N° 737/2022, link and N° 1244/2022 link)	
Innovative device (Y/N)	N
If yes, please indicate which Criteria 1, 2 and 3 are met:	

Summary data		
Request number	**Date of request**	**Applicant**
302	18-10-2023	AOUS Dermatology
Technology		
Device for use as a dressing		

Summary data
The application for Phytostimoline PLUS ADVANCE is essentially an off-label use of DM since the dosage proposed in the two available clinical trials provides therapy for 6 weeks (thus different from the variable duration dosage that the applicant intends to use). In principle, this does not constitute an absolute reason against a positive recommendation. However, it does pose the problem that any long-term therapy (which does not seem to correspond to the applicant's intentions in any case) would inevitably include a period of administration after the patient has been discharged, in which the financial burden of the purchase falls on the patient. A possible approval could be justified by the modest economic impact this DM would have. However, the framework for the use of DM appears ill-defined and also different from the clinical studies supporting DM itself. In conclusion, given that the evidence is scanty and in any case refers to the use of Phytostimoline for 6 weeks, the CO expresses an unfavourable opinion considering the possible evidence in favour of DM to be insufficient. In this decision, the unit price of Phytostimoline PLUS, which appears considerably higher than that of other medicated gauze, plays a major role.
Date of report
14 November 2023
Andrea Messori
Referring pharmacist
Donata Iozzi

BIBLIOGRAPHY

1. Ricci E, Pittarello M. Clinical evaluation of the efficacy and tolerability of a new Rigenase® and polyhexanide-based dressing in the treatment of chronic skin lesions **Italian Journal of Wound Care**, 2022, № 3, https://doi.org/10.4081/ijwc.2022.92

2. Romano E, Campagnuolo C, Palladino R, Schiavo G, Maglione B, Luceri C, Mennini N. Technical Evaluation of a New Medical Device Based on Rigenase in the Treatment of Chronic Skin Lesions. **Bioengineering** (Basel). 2023 Aug 29;10(9):1022. doi: 10.3390/bioengineering10091022. PMID: 37760124; PMCID: PMC10526047.

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APPENDIX: ABSTRACTS OF THE ABOVE REFERENCES

-Study by Ricci et al.

This article discusses the case control of a dressing composed of Rigenase© (plant-derived stimulin) with added polyhexanide, on a new triple-layer PET carrier in the treatment of chronic skin lesions of the lower limb. The aim of the study is the evaluation in terms of repair and control of bacterial bioburden. **Twenty patients were** enrolled with a run-in period of 6 weeks with gold standard therapy, followed by a similar period of treatment with the investigational dressing. The end points were the evolution of the area, measured with an artificial intelligence-based system as primary. Secondary end points: level of infection/colonisation, WBP and pain, all collected using validated scales. The data collected with regard to area showed a statistically significant difference (p<;0.0001). Significant differences were also evident in terms of signs of infection (p<;0.001), WBP score (p<;0.001) and pain with NRS (p<;0.0001). No adverse events or side effects were observed. The authors conclude that the dressing demonstrates a high capacity to stimulate the resumption of reparative phenomena in lesions with a poor tendency to spontaneous repair.

-Study by Romano et al:

Chronic wound is characterised by slow healing time, persistence, and abnormal healing progress. Therefore, serious complications can lead at worst to the tissue removal. In this scenario, there is an urgent need for an ideal dressing capable of high absorbency, moisture retention and antimicrobial properties. Herein we investigate the technical properties of a novel advanced non-woven triple layer gauze imbibed with a cream containing Rigenase, an aqueous extract of *Triticum vulgare* used for the treatment of skin injuries. To assess the applicability of this system we analysed the dressing properties by wettability, dehydration, absorbency, Water Vapor Transmission Rate (WVTR), lateral diffusion and microbiological tests. The dressing showed an exudate absorption up to 50%. It created a most environment allowing a proper gaseous exchange as attested by the WVTR and a controlled dehydration rate. The results candidate the new dressing as an ideal medical device for the treatment of the chronic wound repairing process. It acts as a mechanical barrier providing a good management of the bacterial load and proper absorption of abundant wound exudate. Finally, its vertical transmission minimises horizontal diffusion and side effects on perilesional skin as maceration and bacterial infection.

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Reporting by the Operations Centre, Regional Decree No. 17610 of 7 September 2022.

For further information write to centro.operativo.htart@regione.toscana.it