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Cost-effectiveness analysis for the treatment of Diabetic foot ulcer in France: PRP vs standard of care

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Abstract

Background. Diabetic chronic foot ulcers lead to pain, discomfort and represent a severe economic burden for patients and health systems. The increasing prevalence in diabetes, will lead a higher incidence and costs for Diabetic chronic foot ulcers in next years. Conventional treatment have a rate of healing of around 60/70%. Despite treatment, many chronic ulcers fail to heal or persist for months/years and/or recur after healing, requiring additional advanced wound care therapies for adequate healing. There is an increasing literature showing that platelet rich plasma (PRP) has the potential to improve healing rates over standard care. The clinical results of PRP effectiveness in the treatment of DFU are promising, on the other hand the costs associated with treating DFUs with PRP are presumably higher than using standard therapy.

Objectives. The aim of this work is to carry out an economic evaluation of the use of the Platelet-Rich Plasma (PRP) therapy in the treatment for Diabetic foot ulcer.

Methods. A cost-effectiveness analysis (CEA) were performed using a decision Markov model with a cohort of patients with chronic DFU (duration of >3 weeks) with high orthopaedic risk (neuropathy +/- arteriopathy) and with plantar ulcers 3A (UT classification).

The effectiveness outcomes are reported in terms of Quality Adjusted Life Year (QALY). The costs are reported in Euro (€) currency evaluated in 2018. A micro-costing approach alongside a clinical study was used to assess the resource use. Deterministic sensibility analyses are reported in order to evaluate the robustness of the results and account for the different sources of uncertainty. The analyses have been carried out in the France setting.

Results. PRP treatment for DFU could be considered a cost-effective or even a cost-saving alternative to standard of care in the French setting. The results needs to be interpreted in light of a low level of evidence and calls for more high-quality randomized controlled trials possibly with longer term follow up are required.

KEYWORDS: Platelet-Rich Plasma, Hyaluronic acid, cost-effectiveness analysis, Cost-Utility Analysis, diabetic foot ulcer.

Classification Numbers: C63, D61, I1

1. Introduction

Chronic non-healing ulcer is a major health problem and its prevalence in the world ranges from 1.9 to 13.1% [1-2]. The incidence of chronic ulcers is expected to increase as the population ages and the risk factors for atherosclerotic occlusion such as smoking, obesity and diabetes are increasing. One of the main cause of non-healing ulcer is diabetes. Diabetic foot ulcer (DSU) is diagnosed in 12–18% of patients with type 2 diabetes, and in 0.6–2% of patients with type 1 diabetes [3]. Seventy percent of these patients are diagnosed with peripheral neuropathy [4,5]. Diabetic chronic wounds lead to pain, discomfort, infection, consultations, dressings, hospitalizations, sequelae, sick leaves, and poor quality of life. Moreover become a substantial financial burden for the patient and the healthcare system [6,7]. Individuals with diabetic foot ulcers are susceptible to infection and the healing process is complicated by diabetic neuropathy leading to chronic non-healing ulcers. An estimated 12% of individuals with diabetes foot ulcer require lower extremity amputation [3, 8]. “More than 85% of lower limb amputations are preceded by foot or ankle ulcers and diabetes is one of the major causes of non-traumatic amputations across the world” [9].

In addition, DFU represents an enormous economic burden. The EURODIALE study analysed the direct and indirect annual costs in several European countries (in 14 European centres including Spain, France, UK, Czech Republic, Germany, Denmark, Sweden and Italy) in a total of 821 patients with DFU. The mean annual cost per patient was €10 091, hospitalization being the most relevant direct cost [10]. In Uk, the mean NHS cost of wound care over 12 months was estimated at £7800 per DFU (of which 13% was attributable to amputations), ranging from £2140 to £8800 per healed and unhealed DFU, respectively, and £16 900 per amputated wound [11]. The main cause (around 20%) of total spending are the complications related to DFU [12]. In US, DFU accounted for 83% and 96% of all major and minor amputations related to foot ulcers, respectively, and significantly increased cost of care (DFU: \$1.38 vs. non-DFU: \$0.13 billion/year; $P < 0.001$) [13]. Therefore, it is important to evaluate strategies that ensure better prevention and management wound to lower the number of amputations.

The goal of ulcer treatment is to obtain wound closure as expeditiously as possible. Conventional treatment for non-healing ulcers includes wound cleansing, necrotic tissue debridement, prevention, diagnosis, and, if necessary, treatment of infection, mechanical off-loading, management of blood glucose levels and local ulcer care with dressing application [3, 14]. Therapeutic procedures to manage DFU are fundamentally based on an adequate

covering of the wound, early treatment of the infection, and relief of pressure, with a probability of healing being close to 60% in 1 year, a 40% to 60% rate of recurrence,[15-17] and a 10% to 20% rate of amputations in the short or medium term [15, 18].

Despite treatment, many chronic ulcers fail to heal or persist for months/years and/or recur after healing, requiring additional advanced wound care therapies for adequate healing [19]. It has been demonstrated that plasma growth factor (PGF) such as platelet derived growth factor (PDGF) significantly shortens treatment duration and leads to healing in approximately 80% of wounds [20-24]. Many authors [20-24] found that platelet release has improved healing rates over standard care. On the other hand, others (20-21) found no major difference in healing outcome of leg ulcers, between treatment groups with platelet release and control groups (placebo). An extensive review was performed by Picard et al. 2015. They carried out a PubMed and Cochrane search (1978–2015) including all studies assessing the clinical effect of PRP on the healing of diabetic chronic wounds. The screening retrieved 7,555 articles and 12 studies were included. On six randomized studies included, five found significant benefits for the use of PRP on diabetic chronic foot ulcers. The authors concluded stating that 87.5% of controlled studies found a significant benefit for the adjunction of PRP to treat chronic diabetic wounds. As PRP may be beneficial, they suggest using PRP on diabetic ulcers which remain unhealed after standard treatment [26].

The clinical results of PRP effectiveness in the treatment of DFU are promising [27], on the other hand the costs associated with treating DFUs with PRP are presumably higher than using standard therapy. Therefore, the implementation of this therapeutic approach in health systems should be based on its cost-effectiveness. There is uncertainty about its cost-effectiveness because of the scarcity of published economic studies. To date only few studies directly face the cost-effectiveness of PRP versus standard of care e no economic evaluations in parallel with clinical studies were reported. Two studies prior to 2014 found PRP treatment being cost-effective or even dominant compared with usual care [28-29]. Linertová et al, 2020 found, in a 5 year time horizon, PRP treatment for DFU could be considered a cost-effective or even a cost-saving alternative in Spain, depending on the method of obtaining the PRP (commercial kit versus manual method) and to a large extent on the price of the kit used. Authors called for future studies on the effectiveness and costs of specific devices or methods to be used as inputs for more specific cost-effectiveness models [27].

The objective of this study was to analyse the cost-effectiveness of PRP preparation for the treatment of DFU versus standard of care alongside a clinical study (Le Creusot study) [30]

for providing more specific evidence for clinical and managerial decision making in France setting.

2. Methodology

Model description and Le Creusot Study

The cost-effectiveness analysis was performed using the Markov model, with a hypothetical cohort of patients with chronic DFU (duration of >3 weeks) with high orthopaedic risk (neuropathy +/- arteriopathy) and with plantar ulcers 3A (UT classification). Using a decision-analytical model provides a structure within we can insert evidence from the specific clinical study (Le creusot Study) and also from the literature to generalize the results. The advantage of using markov model is that it is flexible, particularly for modelling chronic diseases and dealing with ongoing risks and events that might happen more than once over time.

The first step was to define DFUs in terms of mutually exclusive states, including all relevant health outcomes, with movement between these states based on transition probabilities. In this study, the Markov model contained six possible health states (2 temporary states, 3 standard states, 1 absorbing state): (1) DFU (first) complete treatment; (2) persistent DFU; (3) Complete healed DFU; (4) Amputation; (5); Post-amputation (6) death from any cause (see Figure 1). At the beginning of the model, patients with DFUs would receive the first treatment according to one of the following strategies: PRP care and usual care. Hypothetical patients started in state 1 and moved into predefined health states. The probability of moving from one clinical state to another during any given cycle of the simulation was described by the transition probability (see tables 1 and 1bis). Each clinical state had an associated cost and effectiveness estimate. Hypothetical patients accumulated costs and QALYs associated with the time spent in each clinical state during the simulated 3 months period. The cycle length was 1 week and the time horizon was 3 months.

In the first state, patients receive their first complete treatment. The first state is a temporary state, therefore patients receive value of cost and utilities for the first treatment and, than go with a 100% probability to the state 2. In state 2 (persistent DFU), they receive the weekly care. Only for PRP treatment there is a certain probability to come back in state one where the full treatment is performed (see table 1). In this way, we model the necessity for some

patients, to have more than one complete treatment. For usual care, this possibility is not allowed since the weekly therapy is equal day by day until the wound is healed.

In state 2, for PRP arm, the home nurse opens the dressing and checks the cleanliness of the primary dressing (from Le creusot study once a week). If the dressing is clean, she will operate the simple repair of the secondary dressing. Otherwise, a second complete treatment is planned. In Le creusot study, a total of 27 patients had one injection, 17 had two injections and 2 patients had three injections. On average a patients received 1.46 injections. Therefore, we modelled a probability of 20% per cycle to receive a second complete treatment. State 2, for usual treatment arm, draw the complex dressing (dressing change) performed by a home nurse every day. Nurse carried out the cleaning and dressing procedure 5 days per week.

Probabilities of healing were informed by the proportion of ulcers completely healed at the 12 weeks time point (Le creusot), 74% for PRP care and 34% for usual care. Whereas Le creusot study showed strong results in favour of PRP, in our cost-effectiveness analysis we also used parameters got from a recent meta-analysis based on five existing clinical trials; the healing success was 58.33% for PRP and 50.31% for usual care [27].

To generalize the model the chance of amputation were included. Amputation is a temporary state leading the post amputation state, it has a penalty of 0.4 QALYs. The probability of amputation was taken from the Moulik study [18] and adjusted according to the model cycles (1 week) [31].

Annual and three month probabilities were transformed to weekly probabilities by the formula propose by Briggs [31]:

$$tp_1 = 1 - (1 - tp_t)^{1/t}$$

Where tp_1 is the weekly transition probability we wish to estimate and tp_t is the overall probability over time period t .

Figure 1: Markov model of diabetic foot ulcer. States are identical for usual and PRP care.

Table 1: Transition Matrix for PRP treatment

	Patient with ulcer	Persistent ulcer	Complete wound closure	Amputation	PostAmputation	death
Patient with ulcer	0.00	1.00	0.00	0.00	0.00	0.00
Persistent ulcer	0.20	0.73	0.07	0.0001	0.00	0.00
Complete wound closure	0.00	0.00	1.00	0.00	0.00	0.00
Amputation	0.00	0.00	0.00	0.00	0.99	0.0029
PostAmputation	0.00	0.00	0.00	0.00	0.99	0.00
death	0.00		0.00	0.00	0.00	1.00

Table 1 bis: Transition Matrix for standard of care

	Patient with ulcer	Persistent ulcer	Complete wound closure	Amputation	PostAmputation	death
Patient with ulcer	0.00	1.00	0.00	0.00	0.00	0.00
Persistent ulcer	0.00	0.94	0.057	0.0001	0.00	0.00
Complete wound closure	0.00	0.00	0.99	0.00	0.00	0.00
Amputation	0.00	0.00	0.00	0.00	0.99	0.0029
PostAmputation	0.00	0.00	0.00	0.00	0.99	0.00
death	0.00	0.00	0.00	0.00	0.00	1.0000

Cost inputs

All costs associated with health states and transition costs in the Markov model were measured in EURO for 2018, as presented in Table 2. Costs were estimated through a micro-costing approach alongside the resources used in the Le Creusot study. The costs are from the perspective of the French healthcare system.

Table 2: Data used in the model

Parameters	Base case value (€)	Range		Data source
		Min	Max	
Nurse/minute (€)	0.30	0.26	0.33	Collective agreement 2019 (Emploi collectif) - (Data refer to the 5ème echelon of Grille indiciaire du grade Infirmier de classe supérieure) Min: (2ème echelon) Max: 8ème echelon of Infirmier de classe supérieure
Blood sampling Tariff (AMI 1,5)	4.725			Conventional tariff applicable to the activity of nurses (Ameli.fr)
<i>Time resources</i>				
Minutes to prepare PRP and dressing (complete procedure) / day	30	25	35	Le creusot study
Minutes for checking the wound treated with PRP / weekly	15	10	20	Le creusot study
Minutes to prepare Hydrocolloid and dressing / daily	20	15	25	Le creusot study

Material used				
RegenKit BCT-1 (X 2)	55	44	75	Market price
RegenKit ATS (X 1)	55	44	75	Market price
<i>Cleaning and Secondary Dressing*</i>				
PRP treatment*	7.33	5.87	8.79	Use PRP 1 day/week
Standard of care*	12.9	10.3	15.5	Use Hydro 5 days/week
Amputation				
Surgery cost	9'721	5'319	14'000	ATIH santé (GHS-DRG)
Annual Post surgery costs	47'000			H. Tchero et al. / Annales d'Endocrinologie
PRP one complete procedure cost	186			
PRP weekly routine check	7.33	5.87	8.79	
Hydrocolloid daily procedure cost	12.6	10.3	15.5	
Probability of healing				
Parameters	Base case ()	Range		References
		Min	Max	
After 12 weeks				
PRP	77%	65	85	Le creusot study
Hydrocolloid	35%	25	45	

After 12 weeks				
PRP	58%	46	69	Del Pino, 2019
Hydrocolloid	50%	40	60	
Utility values				
Parameters	Base case	Range		References
		Min	Max	
No active ulcer	0.84	0.81	0.87	Redekop et al. 2004
Active ulcer	0.70	0.66	0.75	Redekop et al. 2004
One foot amputated	0.68	0.63	0.72	Redekop et al. 2004
Penalty for surgery	-0.4			

For the costs of dressings we have made a number of estimations to get the average price of a simple dressing (PRP group) and complex dressing (usual care). Simple dressing made use of Jelonet, Adaptic, Grassolind plus secondary dressing as serum. Complex dressing, depending on wound characteristics, made used of different families of product. From Le creusot study we have a rate of utilization of 70% of hydrocellular dressing (Mepilex, Ialuset, Urgotull), 20% on superabsorbant hydrocellular dressing (Cutimed, Wlisabord, Sorbact) and 10% using urgostart. In Appendix table 1, we summarize the main parameters used. The details of the calculations on the materials used are included in the Excel file “Couts Materiels Hopital”.

Synthesis of each states:

State 1: DFU (first) complete treatment: (PRP: 186€ comparator: 12.6€)

Note: PRP cost is due to: the use of regenkit BCT-1 (X2) and ATS (X1) + cleaning procedure + the medication + Nurse time. The cost of comparator is due to the cost of Complex dressing + cleaning procedure + Nurse time

State 2: persistent DFU (PRP: 7,3€comparator: 63€)

Note: PRP cost of 7,3€is due to the repair of the medication + Nurse time

The cost of comparator is due to the cost of Complex dressing + cleaning procedure + Nurse time multiplied 5 times per week.

State 3: Complete healed DFU

No cost

State 4: Amputation (9,721€)

Amputation Cost

State 5: Post-amputation (800€)

Post Amputation cost

State 6: Death from any cause

No cost

Utility inputs

Quality of life assessments for the six possible health states were based on the general health status profiles. The general health status profiles are less sensitive respect to illness specific scales, but allow to analyze and compare results also out of the context of a certain disease. A variety of generic preference-based measures have been developed, the most commonly used questionnaires include the EuroQol (EQ)-5D5L, the Short Form 6D (SF-6D) and the Health Utilities Index (HUI). Once completed, the questionnaires generate a score using an algorithm based on values that have been obtained from a sample of the general public [32]. The values are the health-related quality of life (HRQoL) and measure the utility from living in a specific health state. Health states assume HRQoL values between 0 (dead) and 1 (perfect health), negative value are possible when the health status is considered worse than death. QALYs are assessed by combining the weights calculated for health states alongside the time spent in those health states. QALYs represent the number of years lived in perfect health. The advantage of its use is the possibility to compare results among pathologies and among willingness to pay thresholds for health outcome.

In this work quality of life assessments for the six possible health states were based on the generic EuroQol instrument and obtained from a previous published study, as presented in Table 4 [33]. Redekop et al. used a time trade-off method to estimate the utility weights associated with a range of health states related to DFUs and their complications. This source

has also been used previously to provide the quality of life estimates for a cost-effectiveness analysis of a negative pressure device for the treatment of DFUs. QALYs were calculated by multiplying the quality of life utility weight for one health state by the number of years staying in that state.

Sensitivity analysis

Deterministic sensitivity analysis have been conducted to assess the impact of the uncertainty of the parameters used in the model on the results. Deterministic sensitivity analyses are useful to face different uncertainty as: i) model uncertainty, every model it is a simplification of the reality, ii) parameter uncertainty, in the estimation of costs and effectiveness iii) heterogeneity, that is the individual variability between patients. Therefore the sensitivity analyses have been run for the most important parameters of the model (table 2). Deterministic sensitivity analysis (DSA) has been run for every min-max scenario of any parameters. In detail one way DSA have been run for every parameter where a min and max scenario is reported.

3. Results

In the base case scenario PRP results cost saving. The average cost per QALY is respectively around € 80 for comparator and € 58 for PRP. The ICER of PRP introduction is - €17/ QALY that being lower than zero indicate the dominance of the new therapy.

Using the healing probability derived from the meta-analysis the result is confirmed. The average cost per QALY is respectively around € 74 for comparator and € 66 for PRP. The ICER is negative indicating the dominance of the PRP therapy - €4,030/ QALY. The analysis that follow are made using the meta-analysis healing probability data. Initially PRP treatment is more costly, but at each cycle the cumulative costs grow lower than for usual care and from week 7 the comparator become the more costly therapy. This trend is due mainly to less frequency of medications for PRP and to a better healing probability (fig.1).

Figure 1: Cumulative cost per week of the two therapies

To know how each parameter influences the final results one-way sensitivity analysis were performed for the main parameter.

According to the sensitive analysis the ICER calculated is consistent also changing values for the main parameters (see table 3). In the table 3, the variations in the results that would be caused by extreme values of the main parameters are showed. However, no variation of the parameters change the base scenario result, which looks quite robust. The only parameters very sensitive is the number of medications carried out for the comparator and the PRP probability of healing. Using three medications instead of five, we would have PRP no cost saving any more, but cost effective with an ICER of €12,260/QALY. Including the lowest level of PRP healing probability (minus 20% of the base case reported in the meta-analysis) PRP has a negative incremental cost, but also a negative incremental effectiveness.

The analysis unfold as the main difference in costs is due to the daily nurse visits and medication for the comparator therapy, while for PRP therapy we have only one visit per week. The PRP therapy cost is higher in the first week (186€), due to the expense for medical devices and nurse time, but decrease at few euros in the following weeks. Only 20% of patients per week needed a new medication (on average a patient has 1.46 medication in 12 weeks). Therefore, the PRP branch need less nurse time and less use of materials resulting cost saving respect to the hydrocolloid. The PRP therapy is less costly thanks to fewer number of medication and higher probability of healing.

Table 3: Results of one-way sensitivity analysis

Parameters		Incremental Cost	Incremental effectiveness	ICER (\$/QALY)
PRP Healing probability	Min = 0.46	-233€	-0.08	Standard of care
	Max = 0.69	-290€	0.12	Dominated
Hydrogels Healing probability	Min = 0.50			Dominated
	Max = 0.60	-231	0.02	Dominated
Material costs for cleaning and Dressing (PRP)	Min =			Dominated
	Max = 8.79	-248€	0.02	Dominated
Material costs for cleaning and Dressing (Hydrogels)	Min = 10.2	-144€	0.02	Dominated
	Max = 15.5			Dominated
PRP kit Cost	Min			Dominated
	Max = 75€	-146€	0.02	Dominated
Hydrogels weekly number of medication	Min = 3	65€	0.02	12,260

	Max = 6			Dominated
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4. Conclusions

The present study evaluates the cost-effectiveness of PRP treatment compared with usual management of DFU patients in patients with chronic DFU (duration of >3 weeks) with high orthopaedic risk (neuropathy +/- arteriopathy) and with plantar ulcers 3A (UT classification). This work was conducted along a clinical study (Le Creusot Study) allowing a micro-costing approach in the assessment of resource utilization. Effectiveness obtained in the specific study (the healing success was 74% for PRP and 35% for usual care) and, also data from the main meta-analysis were considered (the healing success was 58.33% for PRP and 50.31% for usual care). Under these assumptions, the PRP therapy result cost saving in the base case scenario.

The most important parameters influencing the results are the number of medications and the probability of healing. The study considered the number of medications used in the Le creusot Study. The PRP, after the first complete medication, needs only one intervention per week against five for usual of care. PRP has higher cost for the complete medication, but when the dressing is clean (nurse checks every week) only the simple repair of the secondary dressing is needed. Contrary, when the dressing is not clean a second complete treatment is planned. The probability of a second PRP complete treatment is of 20% weekly. Therefore, PRP has the potential to involve a lower consume of resources (nurse time and materials). As showed in sensitivity analysis considering three medication per week (instead of five) for usual of care, PRP is no longer the cost saving therapy, and with an ICER = €12,260/QALY is cost-effective (ICER inferior to the threshold of 30,000€/QALY). The other important parameter is the probability of healing. PRP to be the cost effective therapy need to have at least 0.55 (versus 0.50 of usual of care) healing probability, otherwise the cost of the new complete medications starts to burden on total cost. Our results confirm the findings of identified economic evaluations (27-29) which found the PRP treatment being cost-effective or even dominant compared with usual care. However, there are few economic evaluations probably because of the scarcity of robust clinical trials and also for the wide heterogeneity in the population enrolled in the studies.

In conclusion, the PRP treatment for DFU could be considered a cost-effective or even a cost-saving alternative in France. The results needs to be interpreted in light of a low level of evidence and complicated by heterogeneity in the characteristics of the patients treated and the procedures used for PRP / usual of care therapies as for example the number of

medication and the type of materials used. Therefore, more high-quality randomized controlled trials, possibly with longer term follow up, are required.

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Appendix

Table 1 Cost of materials used for wound dressing

	Brand	Description	Price	Amount	Unit cost	Coefficient of use	Cost per application
<u>PRP</u>							
jelonet (10x10)	Smith et Nephew	Box of 10	14.38	1	1.43	0.33	0.48
Adaptic (10x10)	Systagenix	boite de 10	22.73	1	2.27	0.33	0.76
Grassolind (10x10)	Hartmann	boite de 10	14.38	1	1.43	0.33	0.48
compresses stériles non tissées		BOITE DE 50 SACHETS X 2	9.31	10 compresses	0.93	1	0.93
serum physiologique		Flacon (250ml)	3.77	1 flacon/10 patients	0.37	1	0.38
steristrip (6 mm x 75 mm)	3M	pochette de 3 bandes	1.43	1 pochette	1.43	1	1.43
Bande adhésive de fixation (10x100)	Lohmann	1 bande	1.44	1	1.44	1	1.44
Bande (7,5x10)	Lohmann	1 bande	1.44	1	1.44	1	1.44
<i>Total medication cost PRP</i>							7.33
<u>Complex dressing</u>							
mediset pansement	Hartmann	boite de 3	11.6	1 set /patient	3.87	1	3.87

post-op							
serum physiologique		Flacon (250ml)	3.77	1 flacon/10 patients	0.37	1	0.38
compresses stériles non tissées			9.31	10 compresses	0.93	1	0.93
Bande adhésive de fixation			1.44	1	1.44	1	1.44
Bande (7,5x7,5)			1.44	1	1.44	1	1.44
betadine gyneco 125ml	Mylan	Flacon	4.11	1 flacon/5 patients	0.82	1	0.82
mépiléx fin transfer (12,5x12,5)	Molnlycke	boite de 10	45.9	1	4.59	0.175	0.80
mépiléx épais (12,5x12,5)	Molnlycke	boite de 10	34.66	1	3.47	0.175	0.60
Ialuset compresse (10x10)	Genevrier	boite de 10	25.73	2	5.14	0.175	0.90
Urgotull (10x12)	Urgo	boite de 16	42.79	2	5.35	0.175	0.94
Cutimed Sorbion (10x10)	BSN médical	boite de 10	21.22	1	2.12	0.07	0.14
Vliwlasorb (10x10)	Lohmann	boite de 10	21.22	1	2.12	0.07	0.14
Sorbact (10x10)	Inresa	boite de 10	21.22	1	2.12	0.07	0.14
Urgostart	Urgo	boite de 16	14.17	2	1.77	0.05	0.08

interface (5x7 cm)							
Urgostart interface (13x12 cm)	Urgo	boite de 16	43.12	2	5.39	0.05	0.27
<i>Total medication cost Complex dressing</i>						<i>1</i>	<i>12.7</i>