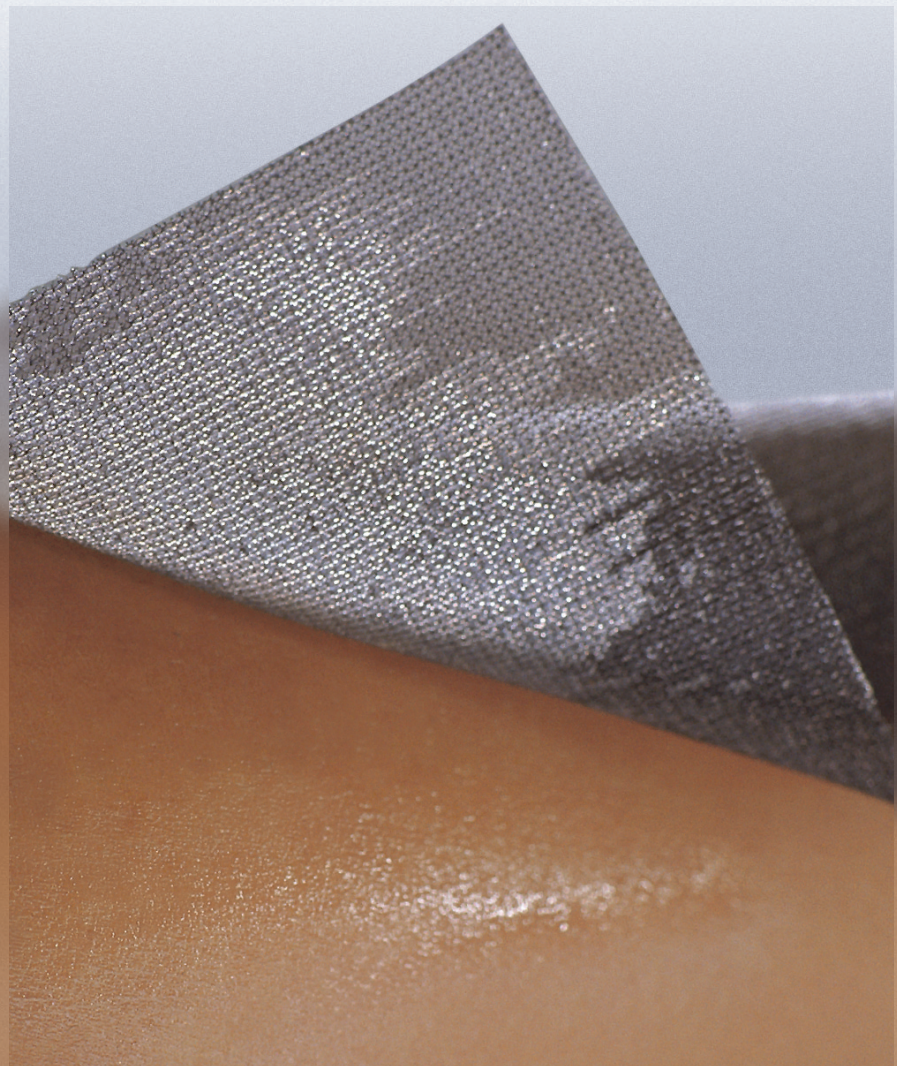




Atrauman[®] Ag – Questions and Answers



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1 Mode of action of silver

1.1 Is the use of silver against bacteria new?

No, silver has been used against bacteria for decades. Since the discovery of antibiotics this application has been forgotten, but for the last few years there has been a genuine "silver renaissance". So, as well as wound dressings, more and more textiles containing silver are being offered.

1.2 How does silver work against micro-organisms?

Metallic silver is not effective against micro-organisms. However, in an aqueous or a moist environment, positively charged particles are given off which are called silver ions (Ag^+). Although the quantity of silver ions released is very small, it is sufficient to kill off bacteria.

1.3 What is the efficacy of silver dependent on?

The quantity of resulting silver ions depends in the main on three factors: the surface, the composition of the surrounding aqueous solution (see point 1.2) and the temperature.

The larger the surface area, the more silver ions are released. For this reason, those products which have an especially large silver surface are very effective against bacteria. As an example, the so-called "nanocrystalline silver" Acticoat (from Smith & Nephew) can be mentioned (see points 2.1 and 2.2).

The higher the temperature, the more silver ions are released. This aspect can be ignored when considering the efficacy of wound dressings containing silver because all wounds have relatively similar temperatures (differences of only a few deg. C).

1.4 Where exactly do the silver ions attack micro-organisms?

Silver ions attack micro-organisms at various places simultaneously, so that build-up of resistance is more difficult. (See point 1.5). The following points of attack have so far been identified:

- the electron transport and therefore the bacteria's energy gain are impeded
- the capability of the bacteria to proliferate is impeded by linkage to the genes (DNA)
- it influences the functions of the cell membranes
- by connecting to important molecules (e.g. enzymes), these are made unable to function, thereby interrupting physiological processes.

1.5 Are there strains of bacteria which are resistant to silver ions?

There are only a few resistant strains of bacteria.

Although build-up of resistance is impeded by the many points of attack, it is however not impossible. There are several reports about silver-resistant strains of bacteria; these references have not been systematically followed up. With this in mind, it can be assumed that silver resistance is of no consequence at present in day-to-day clinical work.

1.6 Are silver ions also effective against fungus?

In higher concentrations, silver ions do also act against fungus. Fungus cells have a different structure to bacteria cells. This causes a much lower sensitivity to silver ions. Generally, much higher concentrations of silver ions are necessary to achieve the same action as against bacteria.

1.7 Do silver ions also act against human cells?

Yes, silver ions are toxic to human cells. However, much higher concentrations are needed to destroy human cells. This is made clear in a comparative study with human skin cells (keratinocytes) in which it was shown that products with a high release rate of silver ions were clearly also more toxic on the cells (see point 3.1.3).

2 Wound dressings containing silver

2.1 In which form is silver integrated into the wound dressing?

Silver is integrated in the wound dressing either in the form of ions or as metal.

It is characteristic for products that contain silver ions that they usually release large quantities of ions very quickly. As a result, bacteria are destroyed very quickly.

A special form is represented by the product Urgotül S.Ag (Urgo). In this case, it is an ointment dressing whose ointment contains silver sulfadiazine. This is a preparation which has been used for burns a long time.

As well as silver ions, the preparation contains an antibiotic sulfadiazine. However, which part of the compound plays which part in the anti-microbial efficacy has not yet been clarified.

Another concept is to integrate metallic silver into the wound dressing thereby taking advantage of the fact that in a moist environment (aqueous solution), silver ions are continually given off from the metallic surface (see point 1.2). In general, these products release comparatively small quantities of silver ions. An exception is Acticoat (Smith & Nephew) which, due to its extremely large metallic surface (nanocrystalline), releases large quantities of silver ions (see point 1.3). In all other cases, the released quantities are relatively small. Typical examples of this product concept are:

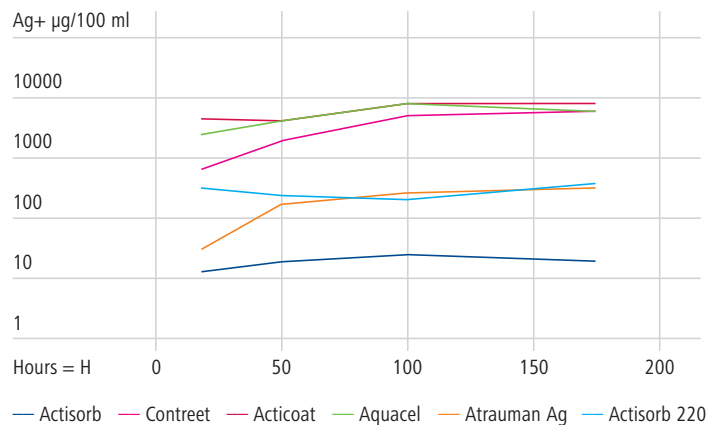
- Acticoat (Smith & Nephew)
- Actisorb silver 220 (Johnson & Johnson)
- SilverCell (Johnson & Johnson)
- Atrauman Ag

The following graph shows example release rates of silver ions from various dressings:

Table: Overview

a) Wound dressings with silver ions	b) Wound dressings with metallic silver
Products	
<ul style="list-style-type: none"> • Contreet H (Coloplast) • Contreet Foam (Coloplast) • Aquacel Ag (ConvaTec) • Urgotül S.Ag (Urgo) 	<ul style="list-style-type: none"> • Acticoat (Smith & Nephew) • Actisorb silver 220 (Johnson & Johnson) • SilverCell (Johnson & Johnson) • Atrauman Ag
Mode of action	
<ul style="list-style-type: none"> • Release of larger quantities of silver ions • Usually quick efficacy (except Contreet H) • Mostly relatively cytotoxic • Reserve of silver ions relatively low 	<ul style="list-style-type: none"> • Release of relatively small quantities of silver ions (except Acticoat) • Develops its efficacy relatively slowly (except Acticoat) • Usually relatively low cytotoxicity (except Acticoat) • Reserve of silver ions is high

Diag. 1: Release of silver ions in wound dressings containing silver



2.2 How do different dressings work?

Dressings that release relatively large quantities of silver ions are also effective in the wound. Yet, it has not been clearly researched how far the efficacy is impeded by salts and molecules in the wound (see point 1.3). Furthermore, there are contradictory statements about how the efficacy of the silver ions is influenced by coatings, necrotic tissue and biofilms (see 2.4). Typical examples of this product category are:

- Acticoat (Smith & Nephew)
- Contreet H (Coloplast)
- Contreet Foam (Coloplast)
- Aquacel Ag (Convatec)
- Urgotül S.Ag (Urgo)

Other dressings have been so formulated that only few silver ions will be released. These products work only when they come into direct contact with bacteria ("touch and kill" mechanism). This happens via the secretion that is absorbed by the dressing. Using this concept, it is assured that no negative influence of the silver ions is brought to bear on human cells in the wound. Typical representatives of this category are:

- Actisorb silver 220 (Johnson & Johnson)
- Atrauman Ag

2.3 Why was Atrauman Ag developed?

The market for an impregnated tulle dressing containing silver opens up an enormous potential for us that can be utilized because of the universal applicability of Atrauman Ag (used in combination with traditional and modern products).

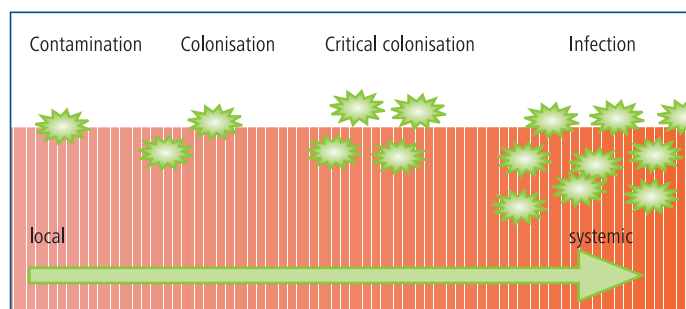
The great advantage of tulle dressing ("Contact layer") is its ability to be used in combination with other dressings. Atrauman Ag can be combined with all available product categories, with hydroactive or more traditional dressings (see point 3.3.2). For a short term silver therapy, the user need not stop treatment with a particular dressing. In short, everyone can continue to use their favourite product, - with a small addition: Atrauman Ag.

2.4 What are the indications for using silver dressings?

Dressings containing silver are suitable for treatment of critically colonised or infected wounds. Dressings containing silver don't, however, replace an antibiotic therapy, they are always only a complementary measure. In addition, dressings containing silver are also suitable for prophylaxis against infection.

A wound is described as "critically colonised" if it is very heavily contaminated by bacteria but not yet infected:

Diag. 2: Process from contamination up to infection



2 Wound dressings containing silver

2.5 What influence do biofilms, coatings and necrotic tissue have on the efficacy of wound dressings containing silver?

Preliminary investigations show that bacteria tend to form “biofilms” in wounds. These are a type of protective coating in which bacteria can proliferate relatively unimpeded by exterior influences. Furthermore, it could be demonstrated that wound dressings containing silver cannot effectively fight bacteria in the biofilms. Necrotic tissue and coatings can have a similar protective effect for bacteria which, in turn, could seriously limit the efficacy of the silver ions in the wound.

With this in mind, it becomes clear that dressings containing silver cannot replace an effective cleansing of the wound (debridement). However, their application can be a useful measure in the course of the total therapy.

2.6 Do dressings containing silver make a debridement superfluous?

No, a debridement is always necessary whether it is surgical, enzymatic or with TenderWet. In this way, devitalised tissue, necrotic tissue and coatings which otherwise would serve as a source of nourishment and protective environment for bacteria, can be cleared away.

The efficacy of silver ions is strongly limited by necrotic tissue and coatings in any case (see point 2.4), so the wound should be well cleaned first and then the dressing containing silver applied as an additional measure.

2.7 Can dressings containing silver replace an antibiotic therapy?

No, wound dressings containing silver cannot replace antibiotic therapy. They are suitable, however, as a complementary therapy (see point 2.4).

3 Atrauman® Ag

3.1 Composition and mode of action

3.1.1 How is Atrauman Ag composed?

The Atrauman Ag support fabric (polyamide) is coated with metallic silver. The silver is bound chemically, i.e. firmly fixed, to the support fabric. The silver coated support material is impregnated with a water-soluble ointment. A formula was chosen which is very similar to the Atrauman ointment (without silver). Both ointments are "triglyceride" based and contain no Vaseline.

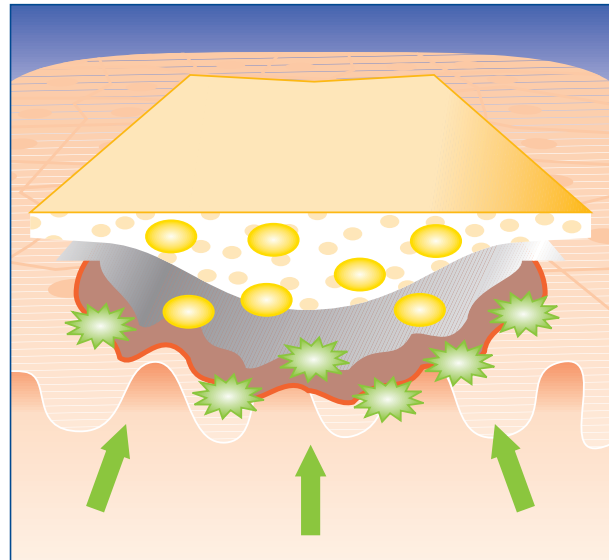
3.1.2 What is the mode of action of Atrauman Ag?

If Atrauman Ag comes into contact with exudate from a wound, silver ions are released from the metallic surface. The quantity of silver ions is relatively small. Consequently, the efficacy of Atrauman Ag is limited to the immediate surroundings. If bacteria come into contact with the dressing, they are destroyed ("touch and kill" mechanism; see also point 2.2).

3.1.3 How do we ensure that a few silver ions only get into the wound itself and do not have a negative effect on the wound healing?

Atrauman Ag contains metallic silver and no silver ions, such as Urgotül S Ag, Aquacel Ag and Contreet, and no nanocrystalline silver as in Acticoat either. The silver ions in Atrauman Ag are produced when contact is made with liquid that is with the exudate. In the process a chemical equilibrium is produced, in which the concentration of free silver ions is kept constant under the conditions given (temperature, composition of the exudates, etc.). Considerably fewer ions are produced in our system than in the competitive products mentioned. As germs float in the exudate, the silver ions attach there first because they have the "shortest distance" to travel here. Of course, silver ions will also get into the wound, but distinctly fewer than in other systems.

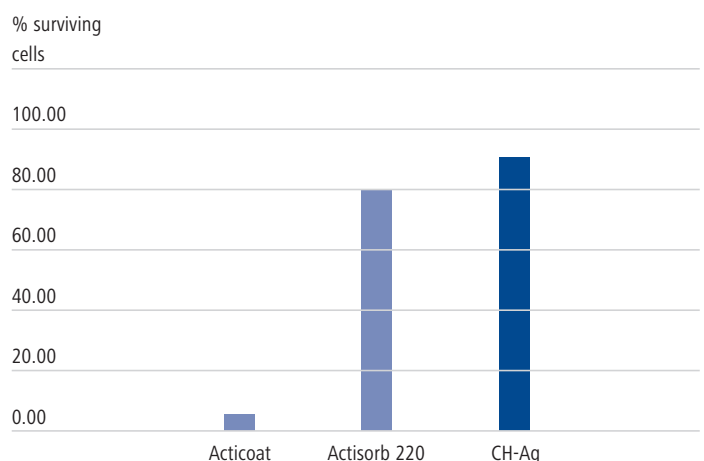
The effect described here can be substantiated experimentally by the agar diffusion and cytotoxicity test. The first test reveals that Atrauman Ag is effective only in direct contact with the bacteria. The second test substantiates the low cytotoxicity of Atrauman Ag.



3.1.4 How cytotoxic is Atrauman Ag?

In a comparative study with human skin cells (keratinocytes) it was demonstrated that Atrauman Ag (= "Ch-Ag" without ointment, i.e. worst case) had a clearly lower toxic effect on the cells than Acticoat which releases considerably more silver ions. In the test, Actisorb, which has a similar release rate showed approximately the same results as Ch-Ag:

Diag. 3: Survival rate of human keratinocytes (1:4 dilution)



(The dilution was chosen to be able to demonstrate the differences optically as well as possible.)

3 Atrauman® Ag

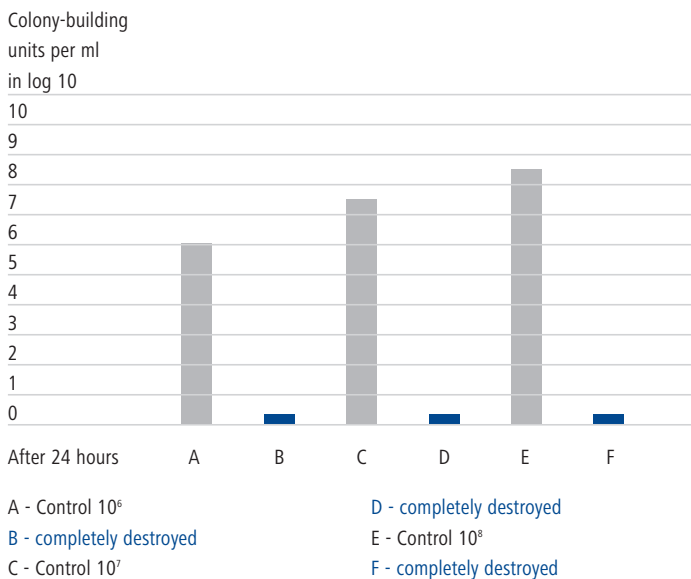
3.2 Microbiological efficacy

3.2.1 What bacteria reductions are achieved by Atrauman Ag?

The quantity of bacteria destroyed generally depends on the test procedure, the solution used, the reaction period and the type and quantity of bacteria. We selected a standard test procedure (method ASTM 2180). The tests were carried out in Ringer's solution with various bacteria in different concentrations over a period of 24 hours.

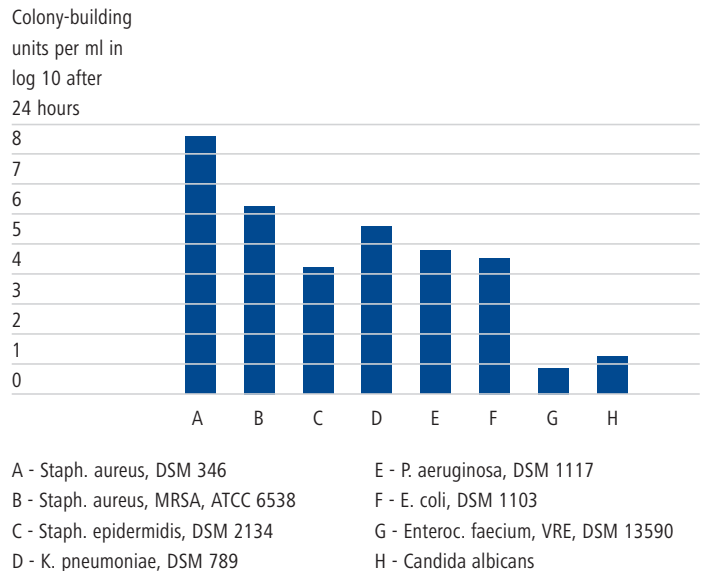
Even with a contamination of 10^7 germs per ml (= 10,000,000), all bacteria were destroyed within 24 hours. It should be borne in mind that a wound which has only 10^5 (= 100,000) bacteria per ml is already considered as infected:

Diag. 4: Results after 24 hour Atrauman Ag treatment



The broad spectrum of activity of Atrauman Ag is demonstrated by the following diagram:

Diag. 5: Atrauman Ag: Germ reduction shown for various types of germs

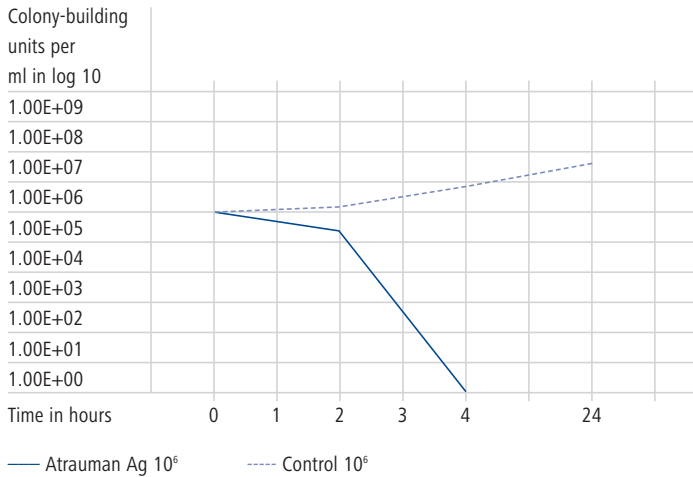


3.2.2 How quickly are bacteria killed by Atrauman Ag?

In this context, it is important to note that wound dressings containing silver do not replace either a debridement or an antibiotic therapy (see points 2.5 and 2.6). That is why the speed plays a relatively subordinate role. Despite this, the efficacy of the dressing should develop in an appropriate time so that the rate of killing exceeds the proliferation rate.

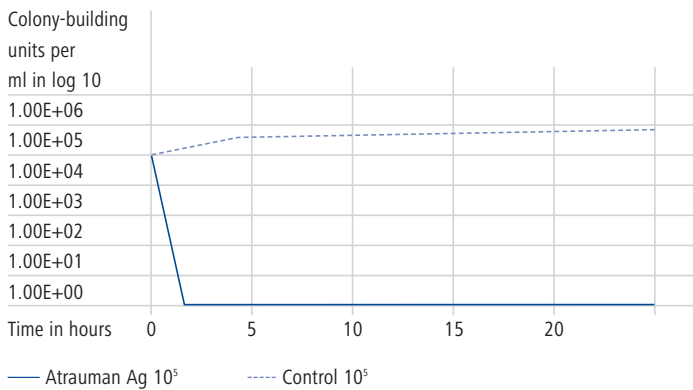
Under the same test conditions (see point 3.2.1), the speed of the destruction depends essentially on the type of germ selected. The following test results show examples for both gram-positive and gram-negative bacteria:

Diag. 6: Bacteria-count reduction shown for *Staphylococcus aureus*



We can see that the gram-positive bacteria “*Staphylococcus aureus*” has been completely destroyed after only four hours – even with a starting count of 10⁶ per ml. In the case of the gram-negative germ “*Klebsiella pneumoniae*” a complete destruction is achieved after only two hours:

Diag. 7: Germ-count reduction shown for *Klebsiella pneumoniae*



3.2.3 Is Atrauman Ag also effective against MRSA (methicillin-resistant *Staphylococci aureus*)?

Yes, Atrauman Ag is also effective against MRSA (methicillin-resistant *Staphylococci aureus*).

Bacteria resistant to antibiotic therapy are becoming more and more of a problem, particularly in hospitals. The most important bacteria in this context is MRSA. Therefore, it is important to know that Atrauman Ag also kills this germ effectively. In Diagram 5 (see point 3.2.1) the results with MRSA bacteria are shown.

3.2.4 Is Atrauman Ag also effective against fungus?

Atrauman Ag is only partly effective against fungus. More than 90% of the yeast fungus *Candida albicans* for instance are destroyed within 24 hours. Even if this is notable, it is much less than the rate of destruction of bacteria (see point 3.2.1; Diag. 4). The reason being that much higher concentrations of silver ions are needed for destruction of fungi.

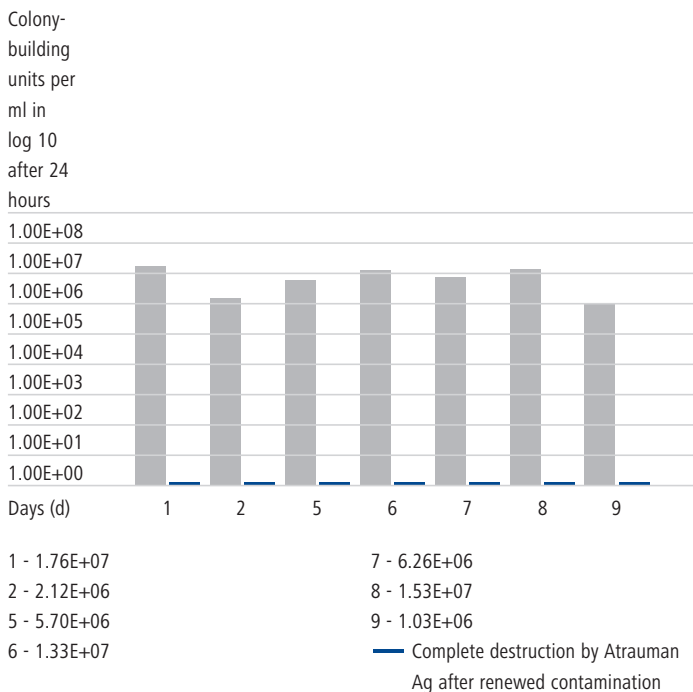
Because a higher release rate would also lead to a higher toxicity on human skin cells, the compromise chosen here is the best solution.

3 Atrauman® Ag

3.2.5 How long does the effect of Atrauman Ag last?

Atrauman Ag is effective for at least seven days. This very careful statement is based on experiments in which Atrauman Ag had been repeatedly contaminated with gram-positive and gram-negative bacteria over a period of nine days. Despite such high contamination, the bacteria were effectively destroyed even after this long period of time:

Diag. 8: Long-term efficiency of Atrauman Ag shown for *Staphylococcus aureus*



3.2.6 Is the efficacy of Atrauman Ag impeded by Ringer's solution?

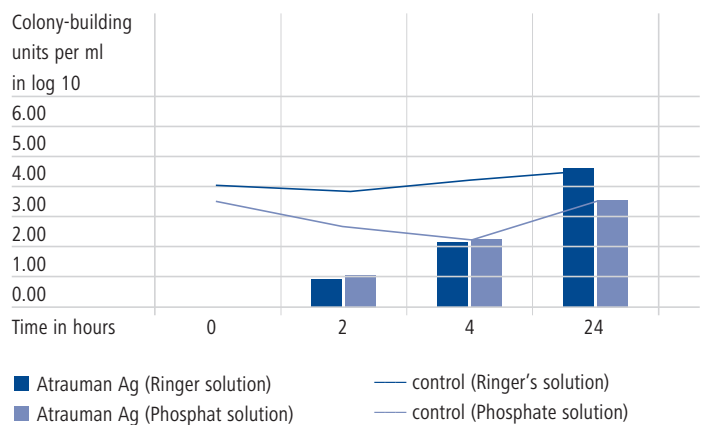
The efficacy of Atrauman Ag is not substantially impeded by Ringer's solution.

It is known that silver ions with chloride ions form a salt which is difficult to dissolve and therefore can only have a limited effect (see point 1.2). Ringer's solution contains relatively large amounts of chloride ions. With this in mind, the question must be asked if Atrauman Ag is also active in Ringer's solution. As all experiments were carried out in Ringer's solution, the answer has to be a clear "yes".

Hence, Atrauman Ag can be used well in combination with TenderWet.

In order to clarify whether Atrauman Ag would be more effective in a solution without chloride ions, a comparative study was carried out with a phosphate buffer. The results clearly show that the efficacy in both solutions did not differ substantially:

Diag. 9: Reduction in germ count shown for *Staphylococcus aureus* in Ringer's solution vs. phosphate solution



3.2.7 Does the triglyceride impregnation prevent the release of silver ions?

The release of silver ions is only reduced to a small degree by the impregnation

The impregnation absorbs moisture very rapidly, so that silver ions can be released. Although the rate of release is higher without the impregnation, it does not lead to a significant difference in the efficacy of Atrauman Ag.

3.3 Application

3.3.1 How is Atrauman Ag applied?

Atrauman Ag is used like any other impregnated tulle dressing, i.e. in combination with a secondary, absorbent dressing. If the wound being treated and the secondary dressing are dry, it is recommended to moisten the secondary dressing with Ringer's solution.

3.3.2 Which secondary dressings can be combined with Atrauman Ag?

In principle, Atrauman Ag can be combined with all important secondary dressings. Tests were carried out to ascertain that Atrauman Ag is antibacterially active in combination with secondary dressings. In particular, the following combinations were tested:

- TenderWet active
- Sorbalgon
- PermaFoam
- Zetuvit
- Gauze swabs

Based on the results, all the combinations listed above can be recommended. The above results may also be transferred to other products of the same category, so that the universal use of Atrauman Ag can be recommended.

3.3.3 Does Atrauman Ag impede the efficacy of TenderWet?

No, because we know from our experience over the years that TenderWet can be combined very well with Atrauman. The cleaning effect is obviously not impeded by this. The advantage of this combination is the fact that the wound edges are protected by the triglyceride based impregnation. It has also been reported many times that this combination alleviates wound pains.

The composition of Atrauman and Atrauman Ag are very similar, so that the results are certainly transferable.

3.3.4 Does Atrauman Ag discolour the wound?

No, the silver in Atrauman Ag does not lead to any discolouration.

Some dressings containing silver tend to discolour the wound to a shade of grey. However, this is only the case when large quantities of silver or silver ions are released. There are for instance recurring reports that Acticoat (Smith & Nephew) is causing discolouration.

Atrauman Ag causes no silver-related discolouration. This is due to the firmly adhered metallic silver and the low quantities of silver ions released. This theory was confirmed in practice by a case study involving 86 patients.

3.3.5 Can Atrauman Ag be cut to size?

Yes, Atrauman Ag can be cut to size by using sterile scissors. As with other dressings, some fluff can occur which is actually harmless. However, due to the dark colour of Atrauman Ag, it is more noticeable than with white products.

3 Atrauman® Ag

3.3.6 Can Atrauman Ag be used for deep wounds?

Yes, Atrauman Ag is equally suitable for use with deep wounds. The dressing has a high integrity and can in all cases be removed from the wound in one piece.

3.3.7 How long can Atrauman Ag be left on the wound?

As a guideline, a period of three days can be assumed. It is not possible, however, to give out a general recommendation, as the optimal dressing change interval depends on many different factors. The first Atrauman Ag case study can offer some guidance here: Atrauman Ag was left on the wound for a maximum period of 15 days, with the average duration being three days.

3.3.8 Can exudate pass through Atrauman Ag unimpeded?

Under normal conditions, exudate can pass through Atrauman Ag unimpeded.

During the Atrauman Ag case studies, the passage of exudate was impeded in less than 5% of the cases. It could not be ascertained whether the cause was connected with Atrauman Ag or not. We have no corresponding reports concerning Atrauman at this point. Knowing that Atrauman and Atrauman Ag have a similar structure, an inference is surely permitted.

In conclusion, we can ascertain that no impediment to exudate passage is caused by Atrauman Ag under normal conditions.

3.3.9 What are the contra-indications?

There are no known contra-indications.

3.3.10 Is Atrauman Ag reimbursed by the health insurance?

Yes, Atrauman Ag, as with every other dressing, is paid for by the health insurance as wound dressing material.

3.3.11 Can Atrauman Ag also be used in case of hypergranulated wounds (exuberant granulation)? After all doctors also use caustic silver sticks.

In this respect, there is no contraindication for Atrauman Ag. However, it will hardly have the effect of the caustic stick ("lunar caustic stick") which contains silver nitrate. Atrauman Ag releases silver ions in low concentration in order to attack germs in the exudate, but not the human tissue.

3.3.12 Can Atrauman Ag be combined with antiseptics or local antibiotics?

We have no data on any interactions between the substances mentioned and Atrauman Ag, which would be difficult to obtain in a laboratory, in any way. If antiseptics or local antibiotics are used, they act against germs so intensively in any case that an argentiferous wound dressing is not required at all.

3.3.13 What does a bronze-coloured discolouration of the tissue mean when using Atrauman Ag?

A bronze-colour discolouration of the tissue caused by Atrauman Ag may occur sometimes, if the product has been subjected to temperatures of more than 50° to 70° C (122° to 158° F). In the meantime, a case has been reported, in which the tissue has discoloured in normal use in a patient. This discolouration has absolutely no significance for the function of Atrauman Ag. As laboratory tests have revealed, the ion release and microbiological effect are not obstructed in any way by the discolouration.

4 Prescription and reimbursement details for Germany

4.1 Is the price of the competitive product Urgotül S Ag from Lauer-Taxe (German database which obtains a view of all the information associated to each medical product) evaluated or determined differently because it is a drug (contains an antibiotic)?

No, it is not. Since 1st January 2004 no differentiation is made between medical products and drugs in this respect. Urgotül S Ag is not subject to the German Drug Price Regulations.

4.2 Is Atrauman Ag really a standard medical supply for general practitioners?

Yes, it is. In all German federal states Atrauman Ag is part of the regular medical products supply for doctor's consulting rooms.



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www.hartmann.info



Presentations	Size	Unit	Code No.	PIP-Code	Units per Case
Atrauman® Ag	5 x 5 cm	pack of 3	499570	2813859	12
	5 x 5 cm	pack of 10	499571	2813842	6
	10 x 10 cm	pack of 3	499572	2813813	12
	10 x 10 cm	pack of 10	499573	2813807	6
	10 x 20 cm	pack of 3	499574	2813687	12
	10 x 20 cm	pack of 10	499575	2813150	6