Extravasation guidelines 2007

Introduction to the Extravasation guidelines

Introduction 4
Overall Goal 4
Specific Targets and Aims 4
The Nurse’s Role 5

Key points to understand from the extravasation guidelines

What is extravasation? 6
Types of extravasation 6
When does extravasation occur? 8
Prevalence 8
Risk factors 8
What are the implications of extravasation? 10
Initial symptoms 10
Tissue damage 10
Surgery 11
Impact on cancer therapy 11
Other consequences 11
How is extravasation recognised? 12
Patient reporting 12
Visual assessment 13
Checking the infusion line 13
Distinguishing extravasation vs. other conditions 14
How is extravasation prevented? 15
Standard procedures 15
Training 15
Patient education 16
Equipment selection 16
Vein selection in peripheral administration 17
Administering intravenous treatment 17
How is extravasation managed? 19
Procedures and protocols 19
Management – initial steps 20
Management – next steps 21
Antidotes 24
Anthracycline extravasation 26
Extravasation kit 26
Surgery and debridement 26
Documentation and reporting 27

Summary 29

appendices 30
List of drugs: vesicants, irritants and non-vesicants 30
Distinguishing extravasation from other conditions 31
Vein selection procedure 32
Administering Savene™ (dexrazoxane) 33
Administering dimethylsulfoxide 34
Administering hyaluronidase 35
Extravasation kit 36
Documentation template 37

References 41

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Introduction

With over 100,000 doses of chemotherapy and in excess of 1,000,000 intravenous (IV) infusions given every day around the world, keeping adverse events and complications of these procedures to a minimum is important both for the patients receiving them and the healthcare systems in which they take place.

Extravasation is a serious condition that warrants special attention from the healthcare professionals involved in administering intravenous medications. This educational module summarises and explains the most recent literature and recommendations on extravasation in the clinical setting – from prevention and recognition to possible treatment with antidotes. It also provides an outline of the pivotal role that nurses play in the patient management process.

The scope of this document is to describe and explain the prevention, recognition and management of extravasation in general terms. More detailed descriptions of techniques for proper cannulation or phlebotomy (an important skill for the prevention of extravasation) will not be dealt with in this guideline.

Overall Goal

Specific Targets and Aims

The Nurse's Role

Overall Goal

The overall goal of these guidelines is to help nurses understand and recognise extravasation, and improve the prevention and overall management of extravasations in cancer patients.

Specific Targets and Aims

The targets and aims of this module are to:

- Increase nurses’ knowledge of specific elements of extravasation:
  - Causes and risk factors for extravasation
  - Features and symptoms of extravasation
  - Differences vs. flare and other reactions
  - Consequences of extravasation
  - Prevention measures
  - The use of antidotes in treating extravasation
- Encourage successful management of extravasation
- Update and inform nurses of the current standards from different guidelines and protocols
- Encourage adoption of procedures for extravasation that fit with the current guidelines
The Nurse’s Role

Nurses are among the best placed professionals to recognise and deal with extravasation in the clinical setting. The nurses who routinely provide cancer therapies intravenously (either peripherally or through central venous access devices (CVADs) are particularly important in the ongoing management of this possibly serious complication of therapy.

Nurses have a key role to play in identification and management of extravasation, and, of course, in preventing it. From maintaining a high standard of care in the delivery of IV drugs to managing the treatment strategy for extravasation, they have many important duties in this area.

Nurses represent an important link for ensuring that extravasation is prevented, diagnosed and managed where possible. Their role in providing information and providing ongoing support for patients relating to cancer therapy (and the need to be vigilant for any symptoms) is critical in cutting the incidence of extravasation.

This module will discuss the role of the nurse in extravasation management and highlight information and issues that will assist nurses to perform these roles more efficiently.
What is extravasation?

In a general sense, extravasation refers to the process by which one substance (e.g., fluid, drug) leaks into the surrounding tissue. In terms of cancer therapy, extravasation is defined as the accidental leakage from its intended compartment (the vein) into the surrounding tissue. Usually, this occurs when intravenous (IV) medication passes from the blood vessel into the tissue around the blood vessels and beyond.

A broader definition of extravasation includes the resulting injury. Depending on the substance that extravasates into the tissue, the degree of injury can range from a very mild skin reaction to severe necrosis.

Types of extravasation

Extravasation can be classified according to the reaction that is caused by the substance passing into the surrounding tissue. Many different drugs have been classified according to the type of reaction they cause; however, for the purpose of this discussion, we will refer only to cancer therapies. It should be noted, however, that cancer therapies are not the only drugs that cause damage when extravasated, and non-cancer therapies (e.g., aminophylline, calcium solutions, hypertonic glucose, phenytoin, total parenteral nutrition, X-ray contrast media) can be equally as destructive.

Cancer drugs can be grouped into 3 broad categories, based on their potential to cause tissue damage upon extravasation:

- Non-vesicants
- Irritants
- Vesicants

Non-vesicants do not cause ulceration. In fact, if they are extravasated, they rarely produce an acute reaction or progress to necrosis. Irritants, on the other hand, do tend to cause pain at, and around the injection site, and along the vein. They may or may not also cause inflammation. Some irritants do also have the potential to cause ulceration, but only in the case that a very large amount of the drug is extravasated into the tissue.
Vesicants are drugs that have the potential to cause blistering and ulceration and which when left untreated, can lead to the more serious side effects of extravasation such as tissue destruction and necrosis. These drugs can be sub-classified according to the mechanism by which they cause damage, which is also important since it affects the management strategy.

- **DNA-binding**: These drugs are absorbed locally and enter the cells, bind to nucleic acids (i.e., DNA) and precipitate the death of the cell. Following cell death these agents can be re-released to destroy non-cancer cells. They can be divided into 3 categories:
  - Anthracyclines
  - Alkylating agents
  - Others

- **Non-DNA-binding**: These drugs initiate cancer cell death by mechanisms other than binding DNA. They can be divided into 2 groups:
  - Vinca alkaloids
  - Taxanes

For a comprehensive list of vesicants (including all subcategories), irritants and non-vesicants please refer to Appendix 1.
When does extravasation occur?

In an ideal situation, extravasation of vesicant cancer therapies would never occur. Despite the many precautionary measures in place, accidental extravasation does still occur, both from peripheral lines and from CVADs.

Prevalence

Extravasation is not as rare as some people may think. In cancer therapy experts estimate that it accounts for 0.5% to 6.0% of all adverse events associated with treatment. However, when you consider that adverse events with cancer therapy are quite common, the absolute number of extravasations which take place is significant.

Data regarding extravasation from CVADs is more limited. One small study estimated that extravasation occurs about 6% of the time.

Risk factors

Some extravasations can be accounted for by error in the IV procedure, etc. However, patients receiving these cancer therapies may have multiple risk factors that make IV infusion very difficult. For example, cancer patients – with a tendency for thin, fragile and mobile veins – are at higher risk of extravasation than the general population.

In addition to factors relating to the procedure and to the patient, factors associated with the equipment/material used, concomitant medications and the treatments themselves can also increase the likelihood of extravasation. Some of the most common factors known to increase the risk of extravasation are listed below:

- Small blood vessels (e.g., infants and young children)
- Fragile veins (e.g., elderly, cancer patients)
- Hard, sclerosed veins
- Mobile veins
- Impaired circulation (e.g., cannula sited on side of mastectomy, lymphoedema)
- Obstructed vena cava (elevated venous pressure can cause leakage)
- Pre-existing conditions (diabetes, peripheral circulatory conditions like Raynaud’s syndrome, radiation damage)
- Obesity
Trouble reporting symptoms early
- Inability to report stinging/discomfort (e.g., sedated, confused)
- Decreased sensation (e.g., as a result of neuropathy, diabetes, peripheral vascular disease)

Cannulation and infusion procedure
- Untrained or inexperienced staff
- Multiple attempts at cannulation
- Unfavourable cannulation site (e.g., back of hand vs. forearm, close to bone)
- Bolus injection
- High flow pressure

Equipment
- Steel butterfly needle
- Catheter size and type

Treatment
- Ability to bind directly to DNA
- Ability to kill replicating cells
- Ability to cause tissue or vascular dilatation
- pH
- Osmolality
- Characteristics of diluent
What are the implications of extravasation?

In general, extravasation is to be avoided. Even in patients who do not progress to ulcerative and necrotic tissue damage may still experience pain and discomfort, as well as indirect consequences, such as disruption of treatment and committing hospital resources to the management of extravasation. The specific symptoms of extravasation, as well as their wider consequences, are discussed in this section.

### Initial symptoms

The initial symptoms of extravasation occur immediately after the blood vessel has been breached. Depending on the agent and the patient extravasation may be accompanied by discomfort or pain, which can range from mild to intense. Patients often describe the pain as a burning sensation. The pain may be followed, in the next few hours, by erythema and oedema near the injection site. In addition, there may be discolouration or redness of the skin near the site.

The initial symptoms of extravasation are subtle, however, and can be similar for the extravasation of different agents (i.e., irritants vs. vesicants). The progression from these initial symptoms, however, differs greatly for irritants and vesicants – particularly relating to permanent damage to the tissue.

### Tissue damage

Vesicants, by definition, have the potential to cause tissue damage upon extravasation from the vein. Like the initial symptoms, the extent of tissue damage can vary greatly between different treatment regimens and patients. Tissue destruction caused by leakage of vesicants into surrounding tissue may be progressive in nature, and may happen quite slowly with little pain. Induration or ulcer formation is by no means an immediate phenomenon – as it takes time to develop. In general, tissue damage begins with the appearance of inflammation and blisters at or near the site of injection. Depending on the drug and other factors, this can then progress to ulceration, and then in some
cases may progress to necrosis of the local tissue. Necrosis can occasionally be so severe that function in the affected area cannot be recovered and surgery is required.5

If extravasation occurs in the forearm, the damage to tissue includes skin and subcutaneous tissue damage. If the extravasation occurs next to a nerve, ligament or tendon, then the damage can extend to that tissue and have an impact on sensation and function.11

Surgery

If vesicant extravasation is not recognised and dealt with promptly, the tissue damage can become so severe that surgical debridement and plastic surgery (possibly including skin grafting) may become necessary.5 In the event that extravasation does affect nerves, ligaments or tendons, the damage may necessitate more extensive surgery.4

It is estimated that one third of vesicant extravasations give rise to ulceration. This ulceration, in combination with pain and necrosis, can be an indication for surgical intervention.5,12

Impact on cancer therapy

Most extravasation protocols call for the immediate cessation of the drug delivery, followed by measures to prevent further spread of the cancer drug into the tissue.8,13–16 As a result, the delivery of cancer therapy may be delayed until the extravasation is resolved.

Some guidelines specifically address the issue of re-establishment of IV cancer therapy – recommending the establishment of an IV site in another limb.13 However, most guidelines do not specifically address this process.8,14–16

Other consequences

Apart from the physical consequences, extravasation can lead to longer hospital stay, more consultations and increased length of follow-up care; the need for physical therapy; high treatment costs; psychological consequences (e.g., distress, anxiety); and even lost wages.4 In addition, it is not uncommon for hospitals and their staff to be faced with a lawsuit following an extravasation.5

All of these factors contribute to the seriousness of an extravasation, and can add to the toll on the patient, their family and the healthcare system. One of the primary goals of extravasation protocols and guidelines is to educate healthcare professionals about the avoidance of serious complications and preventions of extravasations before patients require surgical processes.
How is extravasation recognised?

It is critical that an extravasation is recognised and diagnosed early. The most effective way to recognise and detect extravasation in its early stages is to be aware of and act on all relevant signs and symptoms. Telltale signs and symptoms can be gathered from patient reports, simple visual assessment of the injection site, and careful monitoring of the IV device. Then, once an extravasation is suspected, it will also be important to rule out other possible conditions, such as flare reaction.4,7

The quality of the nursing assessment during administration can play a key role in minimising frequency and severity, since delays in the recognition and treatment of vesicant extravasation increase the likelihood of developing tissue damage and necrosis.4,17

Since extravasation could have serious consequences, a second opinion is always warranted. If there is any doubt as to whether or not it has occurred, stop and ask for help.

**Patient reporting**

**Visual assessment**

**Checking the infusion line**

**Distinguishing extravasation vs. other conditions**

**Patient reporting**

Patients need to know the possible side effects of the treatments they are receiving. In the case of extravasation, it is recommended that the patient be told about the possible complications and to be aware of any pain/sensation at the site of infusion. Patients should feel that they can report any strange sensations as soon as they arise, so the healthcare team can take these symptoms into account.

The most important patient-reported symptoms for assessing extravasation relate to the sensation around the site of injection – or, in the case of a central line, around the CVAD and surrounding area. Typically these complaints include:8,18

- Pain
- Swelling
- Redness
- Discomfort
- Burning
- Stinging
- Other acute changes at the site of extravasation

None of these are confirmation of an extravasation on their own, but should be treated with concern and warrant further examination, such as testing the patency of the infusion with blood return. In addition, the nature of the complaints should be verified against the signs and symptoms of other possible diagnoses.
Visual assessment

Visual signs, while by no means exclusive to extravasation, do provide useful confirmation for patient reports in suspected extravasation. The common signs, occurring at or around the site of the cannula – or, in the case of central line around the CVAD and the surrounding area – include:

- Early symptoms
  - Swelling/oedema
  - Redness/erythema

- Later symptoms
  - Inflammation
  - Induration
  - Blistering

Importantly, many of these symptoms do not occur immediately upon infusion. Induration and blistering, in particular, tend to appear later in the extravasation process. Therefore, careful monitoring of the site should continue during the infusion time and for some time following an infusion.

Checking the infusion line

Apart from patient reporting and visible symptoms of extravasation, it is possible to determine whether extravasation has occurred by checking the infusion line itself. Verification of the line should be used to help confirm any suspected extravasation (peripheral or central line), if possible.

Signs of extravasation, in relation to the cannula, include:

- Increased resistance when administering IV drugs
- Slow or sluggish infusion
- Change in infusion flow
- Lack or loss of blood return from the cannula

Look for blood return (flashback) upon insertion of the needle. If the needle is in the lumen of the vein, you should notice some blood return. If you confirm blood return, the cannula can be glided carefully into position, ready to stop if met with any resistance.

Brief blood return may be seen if the needle passes through the lumen of the vein and then out the other wall. However, the return will halt once the needle has passed the posterior venous wall. If this occurs, the needle has passed through the lumen and anything infused will be administered straight into the surrounding tissue. The cannula should be removed and the procedure recommenced using another vein, if necessary in another vein above the original site on the same vein (closer to the heart).
Distinguishing extravasation vs. other conditions

Distinguishing between extravasation and other local reactions is an important step in diagnosis. Initially, making the distinction can be very difficult and requires sound clinical judgment. Familiarity with the different symptoms increases the likelihood of appropriate treatment. In the case of extravasation, that means that interventions and management will be initiated at an early stage and help to prevent some of the more serious consequences associated with it.⁴,⁸

Other conditions that resemble extravasation include:⁴,⁷,⁸,¹⁸

- Flare reaction
- Vessel irritation
- Venous shock
- Phlebitis
- Hypersensitivity

The principal differences between extravasation and these conditions relate to the nature and timing of the patient’s complaints, the type and extent of erythema noted and the location and presence of swelling.⁴ A guide describing symptoms and differences between conditions commonly associated with IV infusion can be found in Appendix 2.
How is extravasation prevented?

The most important approach to minimising the consequences of extravasation is prevention.\textsuperscript{12} Healthcare professionals involved in the handling and administration of IV cancer therapies should become familiar with their local procedures and protocols and develop an understanding of the important precautionary steps that should be taken to avoid extravasation and the resulting injuries.

Given this cautious and systematic approach, most episodes of extravasation can be avoided altogether.\textsuperscript{21} The following sections provide advice for good practice and may help prevent extravasation and minimise injury.

Standard procedures

Training

Patient education

Equipment selection

Vein selection in peripheral administration

Administering intravenous treatment

Standard procedures

Local policies and protocols for preventing, identifying risk factors, diagnosis, and managing extravasation represent one of the best ways with which to combat extravasation in the clinical setting. The protocols should be drug specific and be developed with input from the whole healthcare team involved.

If they are already in place, efforts should be taken to make them readily available to all who require them (i.e., those healthcare professionals involved in the administration of IV cancer therapy).\textsuperscript{22} If protocols do not exist, efforts should be made to formally document the local procedures for dealing with extravasations.

There are several examples of existing policies and protocols; some of them can even be found online (see references section).\textsuperscript{2,13–16}

Training

As mentioned above, local policies and protocols are very important for the delivery of quality cancer care. As well as making these documents available, active education of the relevant staff members including doctors, would help to keep the standard of care at a consistently high level across the board.\textsuperscript{18} All staff should be encouraged to regularly review the relevant literature on cytotoxics handling and relating to new agents, as part of their ongoing training.\textsuperscript{22}
Those involved in the administration of IV cancer therapies should be educated on the techniques of IV infusion as well as the local organisational policies for:

- Venous access
- Venous assessment
- Administration of chemotherapy
- Management of extravasation
- Management of hypersensitivity, etc.

Patient education

With regard to extravasation, communication with the patient is very important, since they are being relied upon to report symptoms critical in its recognition.

Using positive language, patients should be told about the nature of the cancer therapy they are receiving and the real possibility of side effects. They should be asked to report any change in sensation, stinging or burning, no matter how insignificant it appears to them. An informed patient can then help to recognise extravasation early and should always be listened to.11

In addition, training relating to meeting the information needs of patients within cancer care, for example presenting a positive approach to delivering information vs. a negative one: “XXX is a possible side effect, but we can’t predict your reaction; most patients take these drugs and tolerate them well.”11

Equipment selection

The choice of equipment/material for administering cancer therapy is important when trying to minimise the risk of extravasation. Important considerations include the size and type of cannula or catheter, and whether to use a subcutaneous device or a central line.

In general, the goal is to choose a needle that is least likely to become dislodged, and one that allows the blood to flow around it. As a rule, it is advisable to use the smallest gauge cannula in the largest vein possible. Specific recommendations include:4,7,12,20

- Use of a small bore plastic cannula (1.2–1.5 cm long)
- For peripheral access, short, flexible polyethylene or Teflon
- Use a clear dressing to secure the cannula – to allow for constant inspection
- Secure the infusion line, but never cover the line with a bandage (the insertion point must always be visible)
Vein selection in peripheral administration

The choice of vein for the infusion is an equally important consideration for the prevention of extravasation. Finding the largest, softest and most pliable vein is the best choice to avoid complications. Some general guidelines include:

- Try to use the forearm, not the back of the hand
- Avoid small and fragile veins
- Avoid insertion on limbs with lymphoedema or with neurological weakness
- Avoid veins next to joints, tendons, nerves or arteries
- Avoid the antecubital fossa (area near the elbow)

For a more detailed overview of vein selection please refer to Appendix 3.

If a first attempt to insert a cannula failed, the second insertion should be made above (closer to the heart) the original site if possible. In general, it is thought that it is best to avoid administering cytotoxic drugs below a previous venepuncture site.

Administering intravenous treatment

In addition to careful selection of equipment and veins for administration of IV cancer therapy, there are many precautions that can be considered during the infusion to help reduce the risk of extravasation.

Starting IV treatment:

- Become familiar with the manufacturers’ recommendations for administration of each treatment
- Dilute drugs to the recommended concentrations and give at the appropriate rate
- Check blood return from the cannula, or CVAD, prior to administration
- Before administering therapy, flush the line with saline (sodium chloride 0.9%) or glucose 5% (as well as between infusions)
- Ensure that the cannula is secure during the administration of drugs – the appropriate dressing (e.g., IV OPSITE 3000, VecaFix or Tegaderm IV) should be used
- Never cover the insertion point (i.e., cover cannula site with a bandage)
- If in doubt, re-cannulate

Monitoring IV treatment:

- Check for swelling, inflammation, redness and pain around cannula site during administration of IV drugs
- Check blood return from the cannula when vesicants are administered
- Question the patient about any possible symptoms (i.e., heat, pain and swelling during administration)
- Do not allow patients receiving intravenous infusions of vesicant drugs to leave clinical area
Considerations for vesicants:8,12

- Whenever possible, always give vesicant drugs into a recently inserted cannula
- Patients receiving repeated doses of potentially harmful drugs peripherally should have the cannula sited at regular intervals – every few days (depending on hospital recommendations)
- Consider the order of the infusions being given – attempt to administer treatments so vesicants present the least risk to the patient
- A CVAD could be considered if veins are very difficult to access. This might minimise the risk of extravasation
- In no case should a butterfly needle be used for any chemotherapeutic infusion
How is extravasation managed?

If extravasation does occur, prevention of serious injury and tissue damage becomes the main focus of those involved in the patient management. Swift action is important to limit the damage caused by the extravasated drug. In general the management of extravasation includes detection (covered in the “How is extravasation recognised?” section), analysis and action.

Procedures and protocols

Management – initial steps

Management – next steps

Antidotes

Anthracycline extravasation

Extravasation kit

Surgery and debridement

Documentation and reporting

If they are already existing, efforts should be made to make them readily available to all who need them (i.e., those healthcare professionals involved in the administration of IV cancer therapy). If protocols do not exist, efforts must be made to formally document the local procedures for dealing with extravasations.

It is highly recommended that all healthcare professionals involved in the administration of IV cancer therapy should be aware of:

- The extravasation policy
- The contents and whereabouts of the extravasation kit and a replacement kit

There are several examples of existing policies and protocols which can be found online.
Specific courses of action depend on the nature of the drug, how much of it has extravasated and where. Delays in recognition and treatment can increase the risk of tissue necrosis.

If extravasation is suspected, treatment should begin as soon as possible as commencing treatment within 24 hours can reduce damage to tissues, however, extravasation may only become apparent 1–4 weeks after the administration.

No matter what the nature of the drug, if extravasation is suspected the initial response remains the same. The most important thing initially is to limit the amount of drug extravasating into the surrounding tissue. Depending on your hospital or centre, there may be prescribed steps and procedures to undertake before any action is taken (i.e., getting a physician’s signature on the extravasation protocol).

In general, the first course of action is to stop the infusion, aspirate as much of the infusate as possible, mark the site and then remove the cannula (while continuing to aspirate from the extravasation site). Elevate the affected limb and administer analgesia if required. If possible take a digital image of the extravasated area. Then, depending on the drug being infused, the correct protocol should be followed to determine the next steps. An example protocol is illustrated in Figure 1.

**Figure 1. Management of extravasation.**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Stop the infusion immediately. DO NOT remove the cannula at this point.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Disconnect the infusion (not the cannula/needle).</td>
</tr>
<tr>
<td>Step 3</td>
<td>Leave the cannula/needle in place and try to aspirate as much of the drug as possible from the cannula with a 10 mL syringe. Avoid applying direct manual pressure to suspected extravasation site.</td>
</tr>
<tr>
<td>Step 4</td>
<td>Mark the affected area and take digital images of the site.</td>
</tr>
<tr>
<td>Step 5</td>
<td>Remove the cannula/needle.</td>
</tr>
<tr>
<td>Step 6</td>
<td>Collect the extravasation kit (if available), notify the physician on service and seek advice from the chemotherapy team or Senior Medical Staff.</td>
</tr>
<tr>
<td>Step 7</td>
<td>Administer pain relief if required. Complete required documentation.</td>
</tr>
</tbody>
</table>

NOTE: STEP 8 onwards appear in Figures 3, 4 and 5, depending on whether the extravasation requires *Localisation and neutralisation* or *Dispersion and dilution*. How to determine which pathway to follow is described in the following sections.
Management – next steps

From this point forward, the nature of the treatment prescribed by the presiding physician or hospital policy will depend on the drug, which has extravasated. Figure 2 shows the decision pathway as it relates to individual treatments.

Figure 2. Decide on appropriate treatment.

If the drug is a non-vesicant, application of a simple cold compress and elevation of the limb may be sufficient to limit the swelling etc. In contrast, the extravasation of a vesicant requires several steps and differs for the various classes of drug. There are two broad approaches to limiting the damage caused by extravasation: localisation and neutralisation; or dispersion and dilution.

Localise and neutralise strategy (Figure 3):

- Use cold compresses to limit the spread of infusate. It used to be thought that cold limited spread through vasoconstriction. In animal models, it appears that cold prevents spread by a mechanism other than vasoconstriction – suggested to be decreased cellular uptake of drug at lower temperatures.
- Consider using antidotes to counteract vesicant actions.
Figure 3. Localise and neutralise.*

NOTE: The initial steps leading to STEP 7 are described in Figure 1.

**LOCALISE AND NEUTRALISE**

**Step 8 – LOCALISE**
Apply a cold pack to the affected area for 20 minutes 4 times daily for 1-2 days.

**Step 9 – NEUTRALISE**
Neutralise the drug by using the specific antidote (if available). The antidote should be given as per the specific directions provided by the manufacturer.
(N.B. Only anthracyclines*, mitomycin C and mustine have specific antidotes – for drugs without antidotes omit step 9)

**STEP 10**
Remove the cannula (delivering the antidote) after confirming no more antidote will be prescribed or given.

**STEP 11**
Elevate the limb.

**STEP 12**
Document the incident using extravasation documentation sheet.

**STEP 13**
Arrange follow up for the patient as appropriate.

*For a detailed list of anthracyclines, please refer to Appendix 1*)
Disperse and dilute strategy (Figure 4): 
- Appropriate for the extravasation of vinca alkaloids
- Use warm compresses to prompt vasodilation and encourage blood flow in the tissues, thereby spreading the infusate around
- Consider using hyaluronidase to dilute infusate

**Figure 4. Disperse and dilute.**

NOTE: The initial steps leading to STEP 7 are described in Figure 1.

<table>
<thead>
<tr>
<th>DILUTE AND DISPERSE</th>
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</table>
| **STEP 8 – DISPERSE**  
Apply a warm compress to the affected area for 20 minutes 4 times daily for 1-2 days. |
| **STEP 9 – DILUTE**  
Give several subcutaneous injections of 150–1500 IU of hyaluronidase diluted in 1 mL sterile water around the extravasated area to dilute the infusate. |
| **STEP 10**  
Document the incident using extravasation documentation sheet. |
| **STEP 11**  
Arrange follow up for the patient as appropriate. |

In addition, measures can be taken to limit inflammation, discomfort and pain:
- A saline flush out technique could also be used – but this approach requires specialist advice
- Corticosteroids can be given to treat inflammation – although there is little evidence to support their use in extravasation
- Antihistamines and analgesics may be required for relief of pain and other symptoms

If the infusate is a non-vesicant, the procedure is similar to localise and neutralise, but does not involve any antidotes. A step-by-step approach for non-vesicants is shown in Figure 5.

It is worth noting that beyond the measures described here, unfortunately, the management of extravasation is not well standardised due to a lack of documented evidence. As such, extravasation and often calls for specialist advice.
Antidotes

Antidotes are agents applied or injected to the extravasated area to counteract the effects of the infiltrated agent – usually vesicants. They form an important part of the “localise and neutralise” and the “disperse and dilute” strategies. For example, Savene™ (dexrazoxane) can help to neutralise anthracyclines; whereas hyaluronidase helps to facilitate the dilution of vinca alkaloids into the surrounding tissues. Provided they are used in the appropriate way and for the appropriate infusate they might help to prevent progression to ulceration, blistering and necrosis. The evidence supporting the use of different antidotes is often inconclusive and their use (including pros and cons) should be carefully considered.

Antidotes currently available used for treating extravasation (and their proposed mechanism) include:12,24–28

- Savene™ (dexrazoxane): The only registered antidote for anthracyclines, inhibits DNA topoisomerase II, which is the target of anthracycline chemotherapy, blocking the enzyme so it is no longer affected by anthracyclines and damage to the cells is averted
- Dimethylsulfoxide (DMSO): Prevents ulceration. May work by virtue of its free radical scavenging property
- Sodium thiosulfate: Prevents alkylation and subsequent destruction in subcutaneous tissue by providing a substrate for alkylation
- Hyaluronidase: Breaks down hyaluronic acid (“cement”) in connective/soft tissue, allowing for dispersion of the extravasated drug, thereby reducing the local concentration of the damaging agent and increasing its rate of absorption
Table 1. Antidote use after extravasation.12*

<table>
<thead>
<tr>
<th>Extravasated drug</th>
<th>Suggested antidote</th>
<th>Level of evidence</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Savene™ (dexrazoxane)</td>
<td>Efficacy in biopsy-verified anthracycline extravasation has been confirmed in</td>
<td>3 day course of Savene™ treatment: 1000 mg/m² IV as soon as possible (no later than 6 hours) after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinical trials</td>
<td>extravasation on day 1; 1000 mg/m² on day 2; and 500 mg/m² on day 3 See Appendix 4 for full</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>details</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Topical DMSO (99%)</td>
<td>Suggested as a possible antidote in many literature sources. Due to lack of</td>
<td>Apply locally as soon as possible. Repeat every 8 hours for 7 days See Appendix 5 for full</td>
</tr>
<tr>
<td></td>
<td></td>
<td>evidence it is recommended that this is further studied</td>
<td>details</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Topical DMSO (99%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechlorethamine (Nitrogen</td>
<td>Sodium thiosulfate</td>
<td>Due to lack of evidence, this antidote is not recommended</td>
<td>2 mL of a solution made from 4 mL sodium thiosulfate + 6 mL sterile water for subcutaneous injection</td>
</tr>
<tr>
<td>mustard)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Hyaluronidase</td>
<td>Suggested as a possible antidote in many literature sources. Due to lack of</td>
<td>150–1500 IU subcutaneously around the area of extravasation See Appendix 6 for full details</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Hyaluronidase</td>
<td>evidence it is recommended that this is further studied</td>
<td></td>
</tr>
</tbody>
</table>

*For a detailed list of vesicants, please refer to Appendix 1)
Anthracycline extravasation

For anthracycline extravasation, a new treatment, Savene™, and the data supporting it is changing the way antidotes are recommended in the “localise and neutralise” strategy.

In the past, several protocols and policies suggested the use of topical DMSO (99%) to stop the development of ulcers in anthracycline extravasation. In the past few years, new data from preclinical and clinical studies has changed the way antidotes are used in anthracycline extravasation, particularly that for Savene™. And, it has since become the only licensed specific antidote to anthracycline extravasation.

As a result, more recent guidance in this area recommends the use of Savene™ in the treatment of anthracycline extravasation from both a central- and a peripheral line.

Extravasation kit

The idea behind the extravasation kit is to store all the drugs and equipment that would be used in an emergency situation. The kit should be put together to deal with any eventuality, including extravasation of a variety of vesicant drugs. The kit should be checked regularly and restocked from pharmacy following use.

An example of a recommended extravasation kit can be found in Appendix 7.

Surgery and debridement

Even if extravasation is identified early, progressive extravasation can give rise to ulcerated and necrotic tissue over time. However, the early steps to prevent and manage extravasation help to limit the need for surgery.

Ulcerative cases caused by anthracycline extravasations are common (about ⅓ of all cases), therefore surgery should not be considered as the initial primary treatment of choice. When there is ulceration or continued pain, surgical intervention is indicated to excise the damaged tissue.

In general, the goal of surgery is to remove the damaged tissue and the vesicant infusate to prevent progression of the extravasation, as well as to restore function and reduce pain to the affected area. Once this tissue is removed, the remaining wound often needs to be closed. The options for wound closure include skin flap and skin grafts (from other areas of the body). In most cases, the surgeon would opt for a wait and see conservative approach – to establish whether ulceration will occur naturally and to attempt to avoid surgery and skin grafting. However, in cases where there is pain, surgical debridement of the extravasated area must be considered 24 hours to 1 week after an extravasation.
Each incident of extravasation must be thoroughly documented and reported. Documentation serves several purposes:

- To provide an accurate account of what happened (in the event that there is litigation)
- To protect the healthcare professionals involved (showing they followed procedure)
- To gather information on extravasations, how and when they occurs – for audit purposes
- Highlight any possible deficits in practice which require review

In different centres, the documentation procedure may differ slightly between organisations, however the information collected will be very similar. Following an extravasation, the following details should be documented:

- Patient name and number
- Clinical area
- Date and time of extravasation
- Name of drug which has extravasated
- Signs and symptoms
  - Colour of surrounding skin
  - Size of extravasation
- Description of the IV access
  - Venepuncture site
  - Size and position of cannula
  - Number of attempts at obtaining venous access and positions
  - Drugs administered and the sequence
  - Drug administration technique (bolus or infusion)
  - Blood return
- Extravasation area
  - Approximate amount of the drug extravasated
  - Photograph of extravasated area
  - Size (diameter, length and width) of extravasation area
  - Appearance of extravasation area
- Step-by-step management with date and time of each step performed and medical notification
  - Aspiration possible (including amount) or not, location (venous and/or subcutaneous), and amount
  - Cold/heat
  - Antidote
  - Referral details (if any)
In addition to the initial documentation, the extravasated area should be checked and any changes documented every 8 hours. Any oedema, erythema, stinging, burning, pain, or fluid leakage at insertion site should be included in this report.\(^1\)

A couple of examples of extravasation documentation forms have been included for your reference in Appendix 8.
Managing extravasation in accordance with the latest scientific understanding and medical consensus allows for optimal treatment to be delivered across different regions. By following the example set out in this module, which includes the latest information on extravasation and a selection of current protocols and policies from prominent centres, nurses and other healthcare can help to raise the standard of care in cancer therapy.

Nurses have a key role to play in implementing these improvements to practice. As outlined in this module, they have a unique interaction with the patient and play a large part in the administration of IV cancer therapy. By learning how to effectively recognise extravasation and by becoming familiar with all the local protocols for dealing with it, including the use of antidotes nurses can help to minimise the incidence of this complication of cancer treatment.

Nurses also have the opportunity to play a lead role in expanding the use of best practice in this area. They can help to initiate and develop local protocols and policies where there aren't any due to their role in administration of the drugs and thanks to their knowledge of the patient and unique perspective regarding extravasation management.

By helping to broaden the understanding of extravasation and its management across the nursing and other healthcare professions, it is hoped that this educational module will achieve its objective of improving prevention and overall management of extravasations in cancer patients by utilising the latest available evidence.
Appendix 1. List of drugs: vesicants, irritants and non-vesicants\textsuperscript{8,12,15}

<table>
<thead>
<tr>
<th>Vesicants</th>
<th>Irritants</th>
<th>Non-vesicants\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DNA-binding</strong></td>
<td><strong>Possible irritants\textsuperscript{2}</strong></td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Carboplatin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Mechlorethamine (Nitrogen mustard)</td>
<td>Cisplatin</td>
<td>Bortezumib</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Docetaxel</td>
<td>Cladribine</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Irinotecan</td>
<td>Mitoxantron</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Oxaliplatin</td>
<td>Streptozocin</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Paclitaxel</td>
<td>Etoposide phosphate</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Topotecan</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td>Interferons</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td></td>
<td>Interleukin-2</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td><strong>Non-DNA-binding</strong></td>
<td></td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td></td>
<td>Pemetrexed</td>
</tr>
<tr>
<td>Vinblastine</td>
<td></td>
<td>Raltitrexed</td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vindesine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1} Any agent extravasated in high enough concentration may be an irritant.

\textsuperscript{2} There have been few reports of these agents acting as irritants, but there is no clear evidence for this.

NOTE: For those medications that are not considered a vesicant but cause prolonged patient discomfort at the infusion site, it is strongly recommended that a central line be placed.
### Appendix 2. Distinguishing extravasation from other conditions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Flare reaction</th>
<th>Vessel irritation</th>
<th>Venous shock</th>
<th>Extravasation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>Itchy blotches or hives; pain and burning uncommon</td>
<td>Aching and tightness</td>
<td>Muscular wall of the blood vessel in spasm</td>
<td>Pain and burning are common at injection site; stinging may occur during infusion</td>
</tr>
<tr>
<td>Colouration</td>
<td>Raised red streak, blotches or “hive-like” erythema along the vessel; diffuse or irregular pattern</td>
<td>Erythema or dark discolouration along vessel</td>
<td></td>
<td>Erythema around area of needle or around the venepuncture site</td>
</tr>
<tr>
<td>Timing</td>
<td>Usually appears suddenly and dissipates within 30–90 minutes</td>
<td>Usually appears within minutes after injection. Colouration may only appear later in the process</td>
<td>Usually appears right after injection</td>
<td>Symptoms start to appear right after injection, symptoms endure</td>
</tr>
<tr>
<td>Swelling</td>
<td>Unlikely</td>
<td>Unlikely</td>
<td></td>
<td>Occurs often; does not dissipate for several days</td>
</tr>
<tr>
<td>Blood return</td>
<td>Usually, but not always intact</td>
<td>Usually, but not always intact</td>
<td>Often absent</td>
<td>Usually absent or sluggish</td>
</tr>
</tbody>
</table>
### Criteria for vein selection

<table>
<thead>
<tr>
<th>Most desirable</th>
<th>Appropriate choice of venepuncture site</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDEAL VEIN / BEST LOCATION</td>
<td>forearm</td>
</tr>
<tr>
<td>large, soft, resilient veins in forearm</td>
<td></td>
</tr>
<tr>
<td>IDEAL VEIN / LESS DESIRABLE LOCATION</td>
<td>hand</td>
</tr>
<tr>
<td>large, soft, resilient veins in hand/antecubital fossa</td>
<td></td>
</tr>
<tr>
<td>SATISFACTORY VEIN / BEST LOCATION</td>
<td>forearm</td>
</tr>
<tr>
<td>small, thin veins in forearm</td>
<td></td>
</tr>
<tr>
<td>SATISFACTORY VEIN / UNDESIRABLE LOCATION</td>
<td>hand</td>
</tr>
<tr>
<td>small, thin veins in hand; veins in forearm not palpable or visible</td>
<td></td>
</tr>
<tr>
<td>UNSATISFACTORY VEIN / UNDESIRABLE LOCATION</td>
<td>consider central venous line</td>
</tr>
<tr>
<td>small, fragile veins, which easily rupture in forearm/hand</td>
<td></td>
</tr>
<tr>
<td>UNSATISFACTORY VEIN / UNDESIRABLE LOCATION</td>
<td>consider central venous line</td>
</tr>
<tr>
<td>veins in forearm/hand not palpable or visible</td>
<td></td>
</tr>
</tbody>
</table>

---

*Assess veins in both arms and hands
Do not use veins in compromised limbs/lower extremities*
Appendix 4. Administering Savene™ (dexrazoxane)

Savene™ is the only licensed treatment for anthracycline extravasation (doxorubicin, epirubicin, daunorubicin, idarubicin).

Steps for administration:
1) Follow steps for localisation and neutralisation of extravasation (Figure 1 and Figure 3)
2) Administration of Savene™ should begin as soon as possible and no later than 6 hours after the accident
3) Remove ice packs (or other cooling procedures) from the area at least 15 minutes before the administration of Savene™
4) Reconstitute Savene™ with 25 mL sterile water before further dilution in diluent
5) Give Savene™ as an intravenous infusion once daily for 3 consecutive days according to body surface area:
   a. Day 1: 1000 mg/m²
   b. Day 2: 1000 mg/m²
   c. Day 3: 500 mg/m²
6) For patients with a body surface area of more than 2.0 m² the single dose should not exceed 2000 mg on day 1 and day 2 and 1000 mg on day 3

Please refer to Savene™ prescribing information for a full list of contraindications, precautions and warnings.
Appendix 5. Administering dimethylsulfoxide

Dimethylsulfoxide (DMSO 99%) is an option for the treatment of extravasation with anthracyclines, mitomycin C, doxorubicin, idarubicin, epirubicin and actinomycin D. DMSO/corticosteroids should not be used.

Steps for administration:
1) Follow steps for localisation and neutralisation of extravasation (Figure 1 and Figure 3)
2) Draw around area with indelible pen
3) Put gloves on
4) Apply thin layer of DMSO topically to the marked area
5) Allow it to dry
6) Apply a non-occlusive dressing
7) This should be applied within 10–25 minutes
8) Check for erythema caused by DMSO

Please refer to DMSO 99% prescribing information for a full list of contraindications, precautions and warnings.

Return to text
Appendix 6. Administering hyaluronidase*27

Hyaluronidase may be indicated for suspected or known extravasation of: dextrose in concentration of >10%; parenteral alimentation solution (glucose or protein); solutions containing calcium or potassium; aminophylline; antibiotics. In addition, there are recommendations for hyaluronidase in response to vinca alkaloid extravasation.12

Steps for administration:
1) Follow steps for dispersion and dilution of extravasation (Figure 1 and Figure 4)
2) Administration of hyaluronidase should begin within 1 hour of extravasation for best results
3) Dilute 150–1500 IU of hyaluronidase in 1 mL sterile water
4) If there is no blood return in the affected IV catheter, consider infusing 0.4 CC of dose directly through the affected IV catheter before removing the catheter and administering the remainder of the dose subcutaneously around the periphery extravasation
5) Use 25 or 27 gauge needle and change after each injection
6) Subcutaneously (or intradermally) inject 1 ml (150 IU) of hyaluronidase as 5 separate 0.2 mL injections around the periphery of extravasation site

* Hyaluronidase is not available in all countries

Please refer to hyaluronidase prescribing information for a full list of contraindications, precautions and warnings.

Return to text
Appendix 7. Extravasation kit

Below is an example of a typical extravasation kit, which included:

- Instant cold pack
- Instant hot pack
  (Or a reusable pack, which can be use for both)
- Antidotes according to local procedures
- 2 mL syringes
- 25 G needles
- Skin disinfectant as per local guidelines (e.g., alcohol swabs)
- Indelible pen for marking the affected area
- Documentation forms
- Copy of extravasation management procedure
- Patient information leaflet

Return to text
Appendix 8. Documentation template

## General extravasation template

### Table of contents

- Extravasation of cytotoxic agents – Documentation (I)
  - Cannula used:
    - Butterfly®
    - Venflon®
    - Other
  - Cannula fixated with:
    - Diameter
  - Site of puncture:
    - Left arm
    - Forearm
    - Antecubital fossa
    - Dorsum of hand
    - Port-a-cath system
    - Central venous catheter
  - Was it necessary to puncture the same limb more than once?
    - Yes
    - No
  - Where – in relation to the original puncture site – was the vein punctured?
    - Proximal
    - Distal
    - Medial/lateral
  - Has the patient any of the following symptoms:
    - Upper blockage to inflow
    - Lymphoedema (same arm)
    - Haematoma (same arm)
  - Sequence of application:
    - Amount: mg
    - Substance or trade name
    - Volume:
    - Extravascular
    - Extravascular drug: ml
  - Estimated volume of extravasated drug:
  - Type of administration:
    - i.v.
    - l.a.
    - Bolus
    - Infusion
    - Infusion pump

---

Supplement for Mader et al., Extravasation of Cytotoxic Agents. © Springer-Verlag Wien 2003
Extravasation of cytotoxic agents – Documentation (II)

Extravasation recognised:  
- During administration  
- Immediately after administration  
- ...... hours after administration  
- ...... days after administration

Date: _________
Day month year

Time of day: .......

Measures:  
- Aspiration of cytotoxic drug possible:  
  - Yes  
  - No

Recommended general and substance specific measures taken:

- Additional measures taken:  
  - Yes  
  - No

Risk factors that may influence wound healing (for example, diabetes mellitus):

Information for/instructions to patient:
(Plastic) surgeon consulted:

- Yes

Next control appointment:

- No

Day month year

Day month year

Documented by: .................................................................

Name in capital letters, please

E-mail: .................................................................

Affiliation: .................................................................
## Extravasation of cytotoxic agents – Documentation (III)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ = Applies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ = Deterioration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>= No change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ = Improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Symptoms after extravasation:
- Pain (burning, stinging)
- Oedema
- Erythema
- Blistering
- Discolouration
- Induration
- Functional impairment
- Ulceration
- Necrosis
- Demarcation
- Formation of eschar
- Infection
- Complete healing

### Extent of extravasation:
- Two biggest diameters in cm

### Measures:
- Conservative measures
- Surgical measures: Excision, Transplantation

### Notes:

---

Supplement for Mader et al., Extravasation of Cytotoxic Agents. © Springer-Verlag Wien 2003
**Specific extravasation template**

**Extravasation of anthracycline**  
**Observation and prescription form**

<table>
<thead>
<tr>
<th>Name:</th>
<th>Height/weight: <em><strong><strong>/</strong></strong></em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth:</td>
<td>Surface (m2): _____</td>
</tr>
<tr>
<td>Telephone number:</td>
<td></td>
</tr>
</tbody>
</table>

**Time of extravasation**

<table>
<thead>
<tr>
<th>Location of Extravasation</th>
<th>Observation Date</th>
<th>Observation Time</th>
<th>Time of extravasation</th>
</tr>
</thead>
</table>

**Describe IV access from which extravasation occurred**

| Aspiration on catheter (yes/no) | |
| --- | |
| Size of the affected area (cm x cm): | x | x | x | x | x | x | x |

**Name of anthracycline diluent**

| Amount of fluid extravasated | ML |
| Amount of anthracycline extravasated | Mg |

**Local ice treatment (yes/no)**

| Other local treatment (yes/no) | |

**Describe symptoms listed below using yes/no or use CTC grades none, mild, moderate, severe**

<table>
<thead>
<tr>
<th>Date</th>
<th>Local swelling</th>
<th>Local redness</th>
<th>Local blistering</th>
<th>Local necrosis</th>
<th>Pain</th>
<th>Sensory disturbances</th>
<th>Skin atrophy</th>
<th>Impaired limb function</th>
<th>Disfigurement</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Savene™ dosage to be administered:**

| Day 1 and 2: | 1000 mg/m², Day 3: 500 mg/m² |

**Savene™ infusion (mg/total)**

| Max surface | 2.0 m² |

**Start time of Savene™ infusion**

| Stop time of Savene™ infusion |

**Signature doctor**

**Signature nurse**

---

*By courtesy of TopoTarget A/S*
References


15. Medical University of South Carolina (MUSC). Work practice policy for personnel dealing with cytotoxic (antineoplastic) drugs. 2005 Revision. Available at: www.musc.edu/fanda/risk/oshp/safetymanual03/cytodrug.pdf.


