Extravasation in Oncology

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CONTENT

Despite careful research and revision, all information is given without guarantee. The following information for the treatment of extravasation is based solely on single case and literature analysis. No standard of treatment will be defined. There are no studies for extravasation treatments available. The responsibility for the application of the below mentioned drugs and the possible countermeasures lies with the treating physician. Please do not hesitate to contact us for advice.

INTRODUCTION

According to current legislation (German Drug Law § 63) pharmaceutical companies are obliged to record all case reports of adverse drug reactions (and any suspicion thereof).

In this context we would like to ask you to report all cases of extravasation in association with a medac product, including suspected extravasations. The report form for suspected cases of extravasation can be found on page 60.

Report to:
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Should you have any questions about a medac product please do not hesitate to contact us for advice.

We would like to thank you for your cooperation in the interest of patient safety. You make an important contribution to the safe use of our products.

GENERAL INFORMATION

Extravasation occurs during injections or infusions when the injection or infusion fluid unintentionally enters the tissue surrounding the punctured vessel instead of the vessel itself. A broader definition of extravasation includes the resulting injury. Depending on the substance that extravasates into the tissue, the injury can range from a mild skin reaction to severe necrosis.
There are no systematic controlled clinical trials for the treatment of extravasation in oncology. Information and treatment recommendations are based on studies in animal models, case reports and local, non-controlled studies.

Symptoms of extravasation

Extravasations cause various, mostly non-specific symptoms that can vary considerably in their severity. Completely asymptomatic courses are also known. Symptoms can occur during the infusion as well as only after a significant delay.[32]

Subjective signs of the patient

- Pain
- Burning
- Stabbing pain
- initially asymptomatic

Objective signs of the patient

- Erythema
- Swelling
- Induration
- Altered infusion flow rate (may not be apparent with infusion pumps).
- Missing or impaired blood return during aspiration (but blood return does not exclude extravasation).
- initially asymptomatic

Port systems / Central venous catheters

Port systems are mainly used for poor venous conditions and for infusions with tissue-necrotising substances over a longer period of time (e.g. 12 - 24 hours).[9,32,64,90]

In principle, their use reduces the risk of extravasation, but extravasations cannot be excluded.[9,32] Among the most common causes are dysfunctional port systems.[56,99] Acute chest pain is an important symptom and may indicate central extravasation. The diagnosis is initially made on the basis of clinical symptoms and should be confirmed radiologically.[90]

In the case of central extravasation, more severe tissue damage and more difficult treatment can usually be expected due to frequent delays in diagnosis and the location of the extravasation.[56]

Damage type

(As per[9,32,64,90])

Substances for intravenous use can be divided into three categories which, depending on their potential, can cause tissue damage in the event of extravasation. Depending on the extravasated substance, they can damage nerves, muscles and vessels and progressively destroy tissue. A highly concentrated solution, an alkaline pH or a larger infusion volume are also considered risk factors.

Vesicants (tissue-damaging) are substances that can cause blisters and desquamation and, if not treated, can lead to more serious consequences such as tissue destruction and necrosis.

Irritants (tissue-irritating) often cause pain at and near the injection site or along the vein. They can also cause inflammation. Some tissue irritants may result in ulceration if large amounts of the substance are extravasated into the tissue.

Non-vesicants (not tissue-damaging) do not cause ulceration. When they extravasate, they rarely cause an acute reaction.

Vesicants	Irritants	Non-vesicants
Cabazitaxel	Bendamustine	Arsenic trioxide
Doxorubicin	Carboplatin	Asparaginase, recombi-nant
Epirubicin	Dacarbazine	Bleomycin
Mitomycin	Etoposide	Bortezomib
Oxaliplatin	Fluorouracil	Folinic acid
Paclitaxel	Gemcitabine	Methotrexate
Vinorelbine	Irinotecan	Pamidronate
	Treosulfan	Pemetrexed
		Topotecan
		Zoledronic acid

Differential diagnosis

(As per[9,29,32,64,90])

	Extravasation	*Thrombophlebitis*	*Local hypersensitivity reaction*	*Recall phenomenon*	*Photosensitisation*
Aetiology	Varies depending on substance, e.g. for doxorubicin DNA Intercalation and free oxygen radicals postulated	Local infection due to deficient sterility, Hypersensitivity to substance or excipients	Immune-mediated	Chemotherapy: After previous extravasation, exacerbation of a reaction at the previous extravasatios site even with correct application. After radiotherapy (radiation recall) Inflammatory reaction at the previously irradiated body stite	Increased skin reaction to sun
Pain/ Burning	Pain or burning at the injection site	Immediate pain during injection at the injection site and proximally along the vein used	Pain in the proximal part of the vein used		
Erythema	Local redness		Redness		Redness
Swelling	Local swelling	Swelling at the injection site			Oedema
Other	No aspiration possible, Reduced infusion rate, Resistance during infusion, complications depending on the location of the infusion (peripheral vs. central) and the substance	Possibly followed by venous thrombosis, sclerosis, Hyperpigmentation	Pruritus, urticaria, rarely anaphylactic reaction, regression usually spontaneous within 1 hour after the end of the infusion and flushing of the vein, does not necessarily reoccur with repeated injection (therefore no contraindication). *Special form:* Adriamycin flare: Erythema, induration and/or pruritus along the vein used, rarely pain or oedema, no improvement after stopping infusion.	Radiation recall: Clinical image of severe sunburn (redness, allodynia, swelling, inflammation, blistering, desquamation, formation of necrosis, discolouration of the skin is possible). Latency up to 15 years	Blistering possible
Example		Bleomycin, dacarbazine, epirubicin, paclitaxel, pamidronate	Bendamustine, bleomycin, etoposide	Anthracyclines, bleomycin, etoposide, gemcitabine, methotrexate, pemetrexed, paclitaxel, vinorelbine	Bleomycin, dacarbazine, fluorouracil, methotrexate

PREVENTION

General preventive measures

(As per [9,32,64,90])

- Administration by trained personnel only, avoid hectic situations, provide adequate lighting conditions
- Informing the patient about possible local reactions and the possibility of extravasation and associated symptoms
- Select appropriate venous access; preferably use thick veins in the middle of the forearm
- Avoid the back of the hand, wrist and crook of the arm (to protect nerves, vessels and tendons)
- Avoid areas with poor circulation (e.g. after mastectomy, lymphoedema of an extremity, irradiated area)
- No multiple punctures of the same vein (possibility of extravasation through the previous puncture site)
- Use flexible, thin venflons (no steel cannulas)
- Securely fix the access, leaving the application site visible
- Consider early placement of a central venous catheter, especially for tissue-necrotising agents, repeated or slow infusions
- For tissue-necrotising substances, establish a new access, a tissue-necrotising substance can be administered simultaneously with a fast running compatible infusion solution via a Y-site adapter, avoid continuous infusions via a peripheral access, do not use infusion pumps
- In polychemotherapy, apply tissue-necrotising substance first
- When administering several tissue-necrotising substances, the substance with the lowest application volume should be administered first
- For position control aspirate blood and flush access with physiological saline solution (caution: not applicable for oxaliplatin due to the risk of precipitation, instead flush with glucose 5%[32])
- Carry out regular visual checks during the infusion
- Flush after the end of the application to prevent cytostatic residues from entering the surrounding tissue

<u>Possible causes of extravasation (examples):</u>

- Infusion under pressure (avoid infusion against resistance)
- Injection into a vein that is still blocked (avoid injection against resistance)
- Unsuitable vein
- Multiple punctures of a vein

Portsystems / Central venous Catheters

The use of a central venous catheter reduces the risk of extravasation, but does not eliminate it completely.[9,32]

Before each injection/infusion, the functionality of the system must be checked by aspiration and flushing. If there is a suspicion of malposition or disconnection, the position must be checked by means of a chest X-ray and, if necessary, contrast medium imaging.[9]

Blood return does not rule out extravasation:

- In aspiration, an extravascularly located catheter tip can slide back into the vein. Thus, blood return occurs even though there is a leak in the vein wall.
- The vein wall may have been perforated by the bevelled cannula tip during puncture, leading to extravasation of the cytostatic drug. There is nevertheless a backflow of blood during aspiration, as the opening of the cannula lumen is in the blood vessel.

Possible causes of extravasation in central catheter systems:[56,64]

- Misplacement of the infusion needle/catheter dislocation
- Retrograde infusion due to fibrin formation/ thrombosis of the catheter
- Disconnection of the catheter from the port reservoir
- Defect of the catheter (e.g. due to unintentional cutting during insertion).

Venous thrombosis is one of the late complications of central venous catheter systems.[64] and should therefore also be monitored.

Patient education

Patients who receive chemotherapy as outpatients or who continue treatment at home after an inpatient stay should receive oral and written information.
The patient should ensure that all connections are secured and that the infusion tubing is tight, yet loose enough under the clothing.
During physical activity, work and housework, the patient should be informed about the risk of the infusion tube being torn or cut or the infusion needle slipping out and what measures to take if this happens.
The patient should check the infusion site 2-3 times a day for swelling, pain, leakage or detachment of the bandage.

OVERVIEW PRODUCTS

Overview

(As per[9,21,59,64,90] and Summary of product chacacteristics)

Substance	Risk of tissue damage	Type of tissue damage	Initial management (S. 42)	Specific measures
Arsenic trioxide (Arsenic trioxide medac)	low	non-vesicant	x	none*
Asparaginase, recombinant (Spectrila®)	low	non-vesicant	x	none*
Bendamustine (Bendamustine medac)	moderate	irritant	x	dry cold
Bleomycin (Bleomedac®)	low	non-vesicant	x	none*
Bortezomib (Bortezomib medac)	low	non-vesicant	x	none*
Cabazitaxel	high	vesicant	x	none*
Carboplatin (Carbomedac®)	moderate	irritant	x	none*
Dacarbazine (Detimedac®)	moderate	irritant	x	Light protection of the affected area*
Doxorubicin (Adrimedac®)	high	vesicant	x	Dexrazoxane i.v. ***OR*** topical DMSO, *if appropriate.* + dry cold
Epirubicin (Epimedac®)	high	vesicant	x	Dexrazoxane i.v. ***OR*** topical DMSO + dry cold
Etoposide (Etomedac®)	moderate	irritant	x	none*
Fluorouracil (Fluorouracil medac)	moderate	irritant	x	none*
Folinic acid (Oncofolic®)	low	non-vesicant	x	none
Gemcitabine	moderate	irritant	x	none*

Substance	Risk of tissue damage	Type of tissue damage	Initial management (S. 42)	Specific measures
Irinotecan (Irinomedac®)	moderate	irritant	x	Flushing of the affected area and application of ice*.
Methotrexate (Methotrexate medac)	low	non-vesicant	x	none*
Mitomycin (Mitomycin medac / mito-medac® / mito-extra)	high	vesicant	x	Topical DMSO + cold
Oxaliplatin (medoxa®)	high	vesicant	x	none, no cold
Paclitaxel	high	vesicant	x	Hyaluronidase*
Pamidronate (Pamifos®)	low	non-vesicant	x	none
Pemetrexed (Pemetrexed medac)	low	non-vesicant	x	none*
Topotecan (Topotecan medac)	low	non-vesicant	x	none*
Treosulfan (Ovastat® , Trecondi®)	medium	irritant	x	none
Vinorelbine (Navirel®)	high	vesicant	x	Flushing of the affected vein, Hyaluronidase s.c. + dry heat
Zoledronic acid (Zoledronic acid medac)	low	non-vesicant	x	none

* In line with various guidelines, the use of dry cold can be recommended (for detailed information, please refer to the respective substance-specific sections).

Arsenic trioxide (Arsenic trioxide medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none[9]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

So far, no cases of extravasation have been described in the **literature**.

No cases of extravasation are available from medac's internal **spontaneous reporting system**.

So far, no typical **differential diagnoses** for extravasations with arsenic trioxide have been described.

Asparaginase, rekombinant (Spectrila®)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

Non-recombinant asparaginase has been used intramuscularly in addition to intravenous use for a long time, so a tissue-damaging effect seems unlikely.[64] Recombinant asparaginase is only approved for intravenous use.

So far, no cases of extravasation have been described in the **literature**.

No cases of extravasation are available from medac's internal **spontaneous reporting system**.

So far, no typical **differential diagnoses** of extravasations with recombinant asparaginase have been described.

Bendamustine (Bendamustin medac)

Risk of tissue damage: moderate

Type of tissue damage: irritation

Initial management: yes (⇒ page 46)

Specific measures: dry cold[12]

Additional information:

Various authors recommend the use of dry cold:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]

The classification as tissue irritant is based on the low pH of the reconstituted solution.[64]

In the literature*, Martin et al.* describe 40 cases of extravasation that occurred with bendamustine, seven of these were severe. Further information on symptoms and treatment of extravasation is not mentioned.[69]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system:** Burning, swelling, oedema and redness of the skin.

Local hypersensitivity reactions[9] as well as local irritation and phlebitis are described as **differential diagnoses** for bendamustine (especially after administration as an i.v. bolus, probably due to the low pH of the reconstituted solution).[64]

Bleomycin (Bleomedac®)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Zusätzliche Informationen:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

In vitro, an increase in the residual activity of bleomycin has been demonstrated after application of heat, so heat application after bleomycin extravasation may increase the risk of tissue damage.[64]

Bleomycin is administered intravenously as well as intrapleurally, intramuscularly and subcutaneously, so a tissue-damaging potential seems unlikely.[64]

So far, no cases of extravasation have been described in the **literature**.

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Swelling and redness.

Differential diagnoses of extravasation with bleomycin include pain at the injection site, thrombophlebitis, local hypersensitivity reactions, photosensitisation, and a recall phenomenon after previous irradiation.[9,17,64]

Bortezomib (Bortezomib medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

So far, no cases of extravasation have been described in the **literature**. Since bortezomib is also administered subcutaneously[19], a tissue-damaging effect seems unlikely.

No cases of extravasation are available from medac's internal **spontaneous reporting system.**

Differential diagnoses of extravasation with bortezomib include catheter- associated complications, pain, phlebitis and erythema at the injection site, and local skin irritation.[19,64]

Cabazitaxel

Risk of tissue damage: high

Type of tissue damage: necrosis

Initial management: yes (⇒ page 46)

Specific measures: none[9]

Additional information:

Kimmel et al. recommend the use of **dry cold:**
15-20 minutes at least 4 times a day for the first 24 hours[59]

In case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy, involve **surgeons**.[9]

So far, no cases of extravasation have been described in the **literature**.

No cases of extravasation are available from medac's internal **spontaneous reporting system.**

So far, no typical **differential diagnoses** of extravasations with cabazitaxel have been described, nevertheless overall limited data compared to other taxanes should be taken into account.

Carboplatin (Carbomedac®)

Risk of tissue damage: moderate

Type of tissue damage: irritation

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]

In the **literature**, *Bertelli et al.* report in their prospective clinical study of 6 patients with carboplatin extravasation and describe successful treatment with the application of DMSO (99%) every 8 h for at least 7 days and dry cold for 1 h 3 times daily for 3 days. Symptoms were not presented in detail, but none of the patients developed ulceration.[15]
Marnocha et al. investigated the concentration-dependent tissue toxicity of carboplatin in mice. Concentrations up to 15 mg/ml were tested. However, a threshold above which clinically significant tissue toxicity occurs could not be determined. Most of the ulcerations that occurred healed within 21 days.[68] Carboplatin is therefore classified as a tissue irritant.

In cases from medac´s internal **spontaneous reporting system**, the following symptoms were reported: Swelling, redness, pain, warm sensation and burning.

Reactions at the injection site such as burning, pain, redness, swelling and urticaria are described as **differential diagnoses** for carboplatin.[24]
Furthermore, lack of blood return, difficulties in continuing the infusion and swelling in the area of the venipuncture site are described under paclitaxel and carboplatin therapy. In subsequent ultrasound examinations of the affected area, subcutaneous perivascular oedema could be visualised in these patients. However, paclitaxel is considered the primary causative agent in the study[78]

Dacarbazine (Detimedac®)

Risk of tissue damage:	moderate
Type of tissue damage:	irritation
Initial management:	yes (⇒ page 46)
Specific measures::	protect affected area from light exposure[32,64]

Zusätzliche Informationen:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.* und *Perez Fidalgo et al.*: 20 (-30) minutes 4 times daily for 1-2 days[21,90]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours[59]

The classification of dacarbazine as a tissue irritant is based on the effect of the degradation products under exposure to light.[64] The infusion solution should be appropriately protected **from exposure to light** during preparation and use. Extravasation may cause local pain and tissue damage.[31]

One case of ulceration following dacarbazine extravasation was reported in the **literature** in a study on risk management of extravasation of cytostatic drugs. The affected patient had not cooled the affected area as advised.[2]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Burning, swelling and redness.

Differential diagnoses of extravasation with dacarbazine include local discomfort at the administration site, thrombophlebitis and photosensitisation.[9,31]

Doxorubicin (Adrimedac®)

Risk of tissue damage: high

Type of tissue damage: necrosis

Initial management: yes (⇒ page 46)

Specific measures:

Dexrazoxane (Savene®)
i.v to unaffected limb, within 6 hours of extravasation; Dosage: 1000 mg/m² each on day 1 and 2, 500 mg/m² on day 3

OR (if no dexrazoxane was applied):

DMSO (99%)
apply 3 times a day for at least 14 days to an area twice the size of the affected area (4 drops per 10 cm², let air dry).
AND
dry cold:
4 times a day for at least 15 min over 24-48h (keep a time interval of at least 15 min to the DMSO application)[3,9,90]

Additional information:

Boulanger et al. and *Perez Fidalgo et al.* recommend the use of **dry cold** for 20 (-30) minutes, 4 times a day for 1-2 days with both dexrazoxane and DMSO.[21,90]
When applying cold in combination with dexrazoxane (same as with DMSO, see above), a **time interval of 15 minutes** must be kept to ensure adequate blood flow.[59,96]

In vitro and in mouse models, an increase in the residual activity of doxorubicin has been demonstrated after application of heat, so heat application after doxorubicin extravasation may increase the risk of tissue damage.[64]

Treatment with DMSO is contraindicated in cases of extravasation of **liposomal anthracyclines.**[9,32]
In case of simultaneous extravasation of **vincristine**, *Mader* recommends first injecting up to 1500 IU of hyaluronidase under local anaesthesia and then applying DSMO; heat or cold application should not be used in this case.[64]

For further information on therapy with **dexrazoxane** and **DMSO,** please refer to the section on SPECIFIC MEASURES and the Savene® SmPC.[96]

To **minimise the risk** of perivenous extravasation, doxorubicin infusion solution is administered over 2-3 minutes via the tubing of a freely running intravenous infusion (0.9% saline or 5% glucose) into a large vein using a butterfly needle. A **stinging or burning sensation** in the area of the infusion needle indicates extravasation and the injection/infusion should be stopped immediately and restarted in another vein.[3]

Extravasation can lead to severe cellulitis, blistering and local necrosis.[3] In case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy, involve **surgeons**[9], skin grafts may be required.[3] The extravasation site should be observed for several weeks[37], as tissue damage may occur even after a prolonged time period due to long residence time in the tissue.[64]

The following symptoms of extravasation are described in the **literature**: mainly immediate burning and pain with subsequent swelling, redness or induration. Hyperpigmentation, necrosis (possibly persisting for months to years), local infections as well as movement restrictions up to loss of function.[38,104] *Kazakova et al.* describe a case of a 24-hour delay in the diagnosis of central doxorubicin extravasation and discuss the currently available literature on anthracycline extravasation. The patient described presented one day after infusion due to pleuritic chest pain and shortness of breath. Extravasation was diagnosed by contrast CT and the affected side of the chest was immediately washed out thoroughly with physiological saline and a lobe of the lung was peeled off. In addition, dexrazoxane was administered i.v. for three days (started 36 hours after extravasation). As a result, the chest pain improved, yet the patient continued to show pain, shortness of breath and chest effusion 3 months later. The authors discuss 3 other cases of central doxorubicin extravasation.[57] Two of the cases also specify the use of dexrazoxane i.v. (once within 6 hours, once within a day) in combination with surgical washout of the thorax with physiological saline. The results were considered favourable in both cases.[4,28] In summary, *Kazkova et al.* recommend prompt surgical washout combined with dexrazoxane therapy, even in cases of delayed diagnosis.[57]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Burning, redness, swelling and pain.

As **differential diagnoses** of extravasation, an "Adriamycin flare" (erythema and hardening in the course of the vein) as well as recall phenomena after previous chemotherapy or radiation are described for doxorubicin.[9,64,104] An erythematous striation along the vein and the appearance of facial redness (flush) may indicate too rapid administration.[3]

Epirubicin (Epimedac®)

Risk of tissue damage:	high
Type of tissue damage:	necrosis
Initial management:	yes (⇒ page 46)
Specific measures:	**Dexrazoxane (Savene®)** i.v to unaffected limb, within 6 hours of extravasation; dosage: 1000 mg/m² each on day 1 and 2, 500 mg/m² on day 3 *OR* (if no dexrazoxane was applied): **DMSO (99%)** apply 3 times a day for at least 7-14 days, let air dry. *AND* **dry cold**: 4 times a day for at least 15 min over 24-48h (keep a time interval of at least 15 min to the DMSO application)[9,90]

Additional information:

Boulanger et al. and *Perez Fidalgo et al.* recommend the use of **dry cold** for 20 (-30) minutes, 4 times a day for 1-2 days when using dexrazoxane as well as DMSO.[21,90]
When applying cold in combination with dexrazoxane (same as with DMSO, see above), a **time interval of 15 minutes** must be kept to ensure adequate blood flow.[59,96]

After extravasation, the patient's pain can be relieved by cooling down the area and keeping it cool, applying hyaluronic acid and DMSO.[40]

In case of extravasation of **liposomal anthracyclines**, treatment with DMSO is contraindicated.[9,32]

For further information on therapy with **dexrazoxane** and **DMSO,** please refer to the relevant sections under SPECIFIC MEASURES and the Salvene® SmPC.[96]
The patient should be closely monitored in the following period, as necrosis may still occur after several weeks.[40]

In case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy, involve **surgeons**.[9]

Symptoms of extravasation reported in the **literature** are usually immediate burning and pain followed by swelling, redness or blistering. Hyperpigmentation, necrosis (possibly lasting months to years) and thrombophlebitis.[8, 33, 46, 87, 94, 102, 105, 106]
Aigner et al. report that the use of dexrazoxane can still be successful several days after extravasation has occurred. One patient was initially treated with topical DMSO after extravasation of epirubicin. Under this the the symptoms worsened, so that 3 days after extravasation, dexrazoxane was started for three days. This resulted in complete healing.[5] In principle, however, the therapy should be started as early as possible, as even if the symptoms are initially mild necrosis can develop during the further course.[46]
Uges et al. describe the case of a patient with central extravasation with cyclophosphamide, fluorouracil and epirubicin. During the infusion of epirubicin, the patient developed acute chest and abdominal pain. After an unequivocal diagnosis by CT, the patient was immediately treated by washing out the thorax with physiological saline solution, administering steroids and dexrazoxane for 3 days. In the further course, the parietal and visceral pleura of the affected lung were removed and finally the condition improved.[103]
Various procedures for the surgical treatment of port extravasations (debridement and flap plasty [49], with vacuum pump therapy, if necessary[87] or immediate explantation of the port, if necessary with a subcutaneous washout procedure[49]) are described in the literature.

The following symptoms were reported in cases from medac´s internal **spontaneous reporting system:** Redness, pain, swelling, skin and subcutaneous inflammation, blistering and necrosis of the skin, including the need for debridement, and wound healing disturbance at the catheter site. Dyspnoea, increased blood pressure and sweating have been reported with intrapleural extravasation.

Differential diagnoses of extravasation with epirubicin include erythema around the infusion site, phlebitis/thrombophlebitis and recall phenomena after previous chemotherapy or radiation.[9,40,104,108]

Etoposide (Etomedac®)

Risk of tissue damage: moderate

Type of tissue damage: irritation (probably due to the excipients)

Initial managment: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]

A positive effect of **hyaluronidase** has only been shown in animal experiments so far.[64]

In animal studies, ulceration due to excipients (e.g. polysorbate 80) was observed after undiluted intradermal administration of etoposide. When diluted, the ulcerations were less pronounced. Occasionally, etoposide is described in the literature as causing tissue necrosis. As there have been no clinical cases of necrosis after etoposide extravasation so far, the substance is classified as a tissue irritant.[64]

In cases from medac´s internal **spontaneous reporting system**, symptoms such as redness, swelling and pain, cellulitis and necrosis were reported.

Differential diagnoses of extravasation with etoposide include recall phenomenon after previous irradiation as well as phlebitis and local hypersensitivity reactions.[9,32,41,64,73]

Fluorouracil (5-FU medac)

Risk of tissue damage: moderate

Type of tissue damage: irritation[42]

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]

In the **literature**, *Bertelli et al.* describe the treatment of peripheral vein extravasation with topical DMSO (99%) (every 8 h for at least 7 days) and dry cold (1 hour 3 times daily for 3 days). Out of five patients with extravasation from fluorouracil, three patients had complete healing after only one week. In the other two patients, prolonged application of DMSO for 2-4 weeks resulted in successful treatment.[15]
Nesti et Kovac report a case of extravasation with central venous administration of fluorouracil. The patient's left thoracic wall was increasingly warm, reddened and swollen. The affected region was cooled and subsequently antibiotics were given due to neutropenia, with improvement.[81]
Hervé et al. describe a case of vagus nerve paralysis with laryngeal paralysis following central extravasation into the surrounding tissue.[53]
Cathcart-Rake et Mowery report pericarditis and cardiac arrhythmias in a patient after a rare complication of intra-pericardial extravasation.[26]
Bostelman describes two cases of central venous extravasation during 48 h continuous infusion of fluorouracil. Both patients experienced non-painful erythema and induration around the catheter/port.[20]
White et Elder also report a case of central venous extravasation after continuous infusion of fluorouracil. There was pain, redness and induration around the port, which was treated with 1% hydrocortisone cream and DMSO lotion. A saddle pulmonary embolism was also diagnosed on CT. However, it remained unclear whether the thrombus was caused by chemotherapy, irritation at the port site or various underlying diseases.[107]

In cases from medac´s internal **spontaneous reporting system**, the following symptoms in particular were reported: Swelling, redness, pain, itching, burning and tingling (with concomitant cisplatin extravasation). In one spontaneous case, adipose tissue necrosis was suspected after extravasation of a larger volume through a low-

lying port system. In another spontaneous case, back pain and dyspnoea were reported after extravasation into the mediastinum.

Differential diagnoses of extravasation with fluorouracil include photosensitisation, itching, erythema and hyperpigmentation. [27,32,42,93] With continuous infusion, there is a high risk of phlebitis.[9]

Folinic acid (Oncofolic®)

Risk of tissue damage:	low
Type of tissue damage:	no tissue damage
Initial managment:	yes (⇒46)
Specific measures:	none

Additional information:

No substance-specific measures can be recommended; folinic acid is not described in the current guidelines for the treatment of extravasations.

One case of extensive fatty tissue necrosis of the breast after folinic acid extravasation is described in the **literature**. As this was diagnosed months after the extravasation, no therapeutic measures were initiated.[47]

In cases from medac´s internal **spontaneous reporting system**, symptoms such as swelling, redness, local hypersensitivity of the skin and pain have been reported.

So far, no typical **differential diagnoses** of extravasations with folinic acid have been described.

Gemcitabine

Risk of tissue damage: moderate

Type of tissue damage: irritation[42]

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

One case of successful treatment after cooling has been reported in the **literature**.[62] *Okuda et al.* describe a case of perivenous extravasation of gemcitabine and cisplatin. Pain and redness were already observed during the infusion, which were subsequently treated with cooling and clobetasol ointment. Nevertheless, necrosis of the dermis occurred 2 weeks later and its the conservative therapy lasted 2.5 months.[82] In an early review article on gemcitabine, *Aapro et al.* also report side effects that occurred in connection with extravasations. They describe pain, bleeding, redness, inflammation, oedema and hypersensitivity at the injection site, among others.[1]

There are no cases from medac's internal **spontaneous reporting system.**

As a **differential diagnosis** of extravasation, recall phenomena after previous chemotherapy or radiation are described for gemcitabine.[9,32,64] Furthermore, reactions at the injection site occur which are mainly mild.[44]

Irinotecan (Irinomedac®)

Risk of tissue damage:	moderate
Type of tissue damage:	irritation (probably due to the excipients)
Initial managment:	yes (⇒ page 46)
Specific measures:	flushing of the affected area and application of ice[55]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]

Cases of extravasation have not been described in the **literature** so far.

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Redness and mild swelling at the injection site.

Reactions at the infusion site are described as a **differential diagnosis** of extravasation with irinotecan.[55]

Methotrexate (Methotrexat medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Zusätzliche Informationen:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

Low-dose methotrexate (MTX) is administered subcutaneously and intramuscularly so that a tissue-damaging effect seems unlikely.[64]
Nevertheless, local side effects (burning sensation) or damage to the injection site (sterile abscess formation, loss of fatty tissue) are described for intramuscular use of high-dose MTX.[72]
For subcutaneous application of low-dose MTX, however, only mild local skin reactions (burning, erythema, swelling, discolouration, severe pruritus, pain) have been observed.[76]

In the **literature,** *Brown et al.* describe a case of peripheral vein extravasation of MTX into the right forearm. This resulted in erythema and swelling of the right upper limb and imaging showed muscle necrosis and microcalcification of the soft tissues.[23]
Manimaran et al. report a case of central venous extravasation with secondary infection due to a (very rare) perforation of the port chamber base. The 4-year-old patient initially developed fever and, during further applications, oedema, erythema and pain in the area of the port chamber. The port was exchanged and further therapy was without complications.[66]

There are no cases from medac's internal **spontaneous reporting system.**

Hypersensitivity reactions, photosensitisation and recall phenomena after previous irradiation are described as **differential diagnoses** of extravasations with MTX.[9,32,64]

Mitomycin (Mitomycin medac / mito-medac® / mito-extra®)

Risk of tissue damage: high

Type of tissue damage: necrosis

Initial management: yes (⇒ page 46)

Specific measures:

After IV Application
DMSO (99%) every 4-8 h, allow to air dry, use for at least 7-14 days or until symptoms have resolved

AND
Dry cold: 4 times a day for at least 15 min over 24-48 h (keep a time interval of at least 15 min to the DMSO application)[9,74]

After instillation into the bladder
none

Additional information:

Extravasation after systemic application:
Extensive necrosis occurs in the affected area after extravasation. Injections should be administered through the tubing of a well and safely running infusion. In case of extravasation, the immediate application of **DMSO** and dry, **cold compresses** is recommended (in case both are applied, ensure a time interval of 15 min[9]). A (plastic) surgeon should be consulted early (within 72 hours). To promote regrowth of the damaged tissue, a systemic **injection of 200 mg vitamin B6** may be helpful.[74]

For further information on therapy with **DMSO**, please refer to the corresponding section under SPECIFIC MEASURES .

Extravasation after intravesical use:
Symptoms of extravasation after intravesical application of mitomycin may occur immediately after application or weeks or months later. It may be unclear whether extravasation is due to an unnoticed perforation, a thinned *tunica muscularis,* or whether the drug was not administered correctly. The first symptoms are pelvic or abdominal pain that are refractory to simple analgesia. In most cases, (fat) tissue necrosis in the surrounding area has been observed as a consequence of extravasation. Bladder perforation or the development of a fistula and/or abscess has also been reported. Therefore, to prevent serious consequences, physicians should consider the possibility of extravasation in patients complaining of pelvic or abdominal pain.[74]

In the **literature**, ulcerations and necroses are reported after extravasation with mitomycin, which occurred both after systemic and intravesical administration, delayed by days to weeks after initially inconspicuous application.[6,7,43,51,79,88,110]
Rentschler et al. report on two patients in whom the injection of vitamin B6 led to a significant improvement in necrosis and pain after mitomycin extravasation.[95]
Several authors report extravasation and serious complications in the abdomen after instillation of mitomycin into the bladder:
Six patients had received mitomycin instillations after unnoticed bladder perforation (retrospectively detected by imaging). The extravasations resulted in pain, recurrent urinary tract infections and ureteral obstruction, some with long-term consequences such as urinary incontinence or persistent pain. The patients were treated with indwelling catheters and three of the patients required further surgery.[39]
In two patients, postoperative instillation of mitomycin resulted in leakage of mitomycin from the bladder without any perforation of the bladder having been visible during surgery. In both cases, the bladder had to be removed.[86]
Leong et al. describe a case of extravasation following bladder perforation, which resulted in a significant inflammatory reaction and severe parapelvic calcifications and fistula formation between the bladder wall and the pelvic sidewall. However, the patient was successfully operated on and subsequently remained symptom-free.[63]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Swelling, redness, pain, abdominal pain, oedema, necrosis, skin lesions, fever, necrosis and perforation of the bladder with bacterial superinfection and pelvic abscess.

Differential diagnoses of extravasation with mitomycin after intravenous administration have not been described yet. Differential diagnoses after intravesical administration include cystitis and local irritation of the bladder wall.[74]

Oxaliplatin (medoxa®)

Risk of tissue damage:	high
Type of tissue damage:	necrosis
Initial management:	yes (⇒ page 46)
Specific measures:	none[9,64] cave: do not apply cold[32,64]

Additional information:

Various authors recommend the application of **dry heat**:

- *Boulanger et al.* and *Perez Fidalgo et al.*: 20(-30) Minuten, 4 times a day for 1-2 days[21,90]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours[59]

Cold is not recommended as it can trigger oxaliplatin-induced neuropathy.[32,64,71]

Do not flush with sodium chloride (due to risk of precipitation), **if flushing** is indicated, **glucose 5%** should be used.[9,32,64]

Extravasation can cause local pain and inflammation that can be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein.[11,58,71,91]

Therefore, **surgeons** should be consulted in case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy.[9]

In the **literature**, *Kretzschmar et al*. report five cases in which extravasation of a moderate to high dose of oxaliplatin corresponded to the clinical picture of erysipelas. In none of the cases necrosis occurred. In two of the patients, high- dose oral dexamethasone (8 mg, 2 x daily for several days) was used to treat the inflammation and seemed to have a positive effect on the severity of the inflammation.[60]
In one case with significant tissue damage and clinical signs of infection such as fever, the administration of antibiotics was not successful. Slow, almost complete healing occurred only after intensive physiotherapy with lymphatic drainage and prednisone administration.[18]
In another case, after extravasation, 1500 IU of hyaluronidase were injected, the region was cooled, 1% hydrocortisone cream was applied and anti-inflammatory

drugs and oral analgesia including morphine derivatives were given. This resulted in complete healing.[70]
In the case of port extravasation, immediate explantation of the port, if necessary with a subcutaneous washout procedure, as well as debridement and flap plasty, if necessary, are described in the literature.[49]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Swelling, redness, blistering, overheating of the skin, fever, induration, pain, nerve pain, tingling, inflammation and necrosis. In one case, shortness of breath, mild chest pain and bilateral pleural effusions were reported after extravasation of oxaliplatin into the mediastinum.

Reactions at the injection site (local pain, redness, swelling and thrombosis) are described as **differential diagnoses** ofextravasation with oxaliplatin.[71]

Paclitaxel

Risk of tissue damage:	high
Type of tissue damage:	necrosis
Initial managment:	yes (⇒ page 46)
Specific measures:	subcutaneous or intradermal perilesional injections with **hyaluronidase** (off-label use) dosage: 1-10 ampoules of 150 IU (depending on the size of the affected area) under adequate analgesia [9,64] no thermotherapy required[9]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.:* 20-30 minutes, 4 times a day for 1-2 days[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours [59]

Heat is not considered beneficial.[32]

For further information on therapy with **hyaluronidase**, please refer to the corresponding section under SPECIFIC MEASURES .

In case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy, involve **surgeons**.[9]

Immediate reactions such as redness or oedema are described in the **literature**, but other symptoms such as pain, induration, inflammation, cellulitis, lesions with ulceration, discolouration, skin detachment, paraesthesia or necrosis may possibly occur several days after initially inconspicuous extravasation.[16,52,98]
This delay in the onset of extravasation symptoms is facilitated by the high molecular weight, protein binding and tissue persistence of paclitaxel.[98]
Recall phenomena at sites of previous extravasation may still occur several weeks after re-infusion at a different site.[54]
Haslik et al. described the explantation of the port with debridement and flap plasty after port extravasation.[49]

In cases from medac's internal **spontaneous reporting system,** symptoms such as erythema, localised warm sensation and swelling have been reported.

Reactions at the injection site (local oedema, pain, erythema and induration), thrombophlebitis and recall phenomena after previous chemotherapy or radiation are described as **differential diagnoses** of extravasation with paclitaxel.[9,54,75,97,100]
In the vast majority of cases, thrombophlebitis is not caused by paclitaxel itself but by excipients.[64]
In some cases, these reactions occur during a prolonged infusion period or delayed after one week to 10 days.[100]
Furthermore, during paclitaxel and carboplatin therapy, lack of blood return, difficulties in continuing the infusion and swelling in the area of the venipuncture site were described. In subsequent ultrasound examinations of the affected area, subcutaneous perivascular oedema could be visualised in the patients. Paclitaxel is considered the primary causative agent in the study.[78]

Pamidronate (Pamifos®)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measures: none

Additional information:

No substance-specific measures can be recommended; bisphosponates are not described in the current guidelines for the treatment of extravasation.

Cases of extravasation in humans have not yet been described in the literature, although pamidronate has been used for decades. Due to this limited data on long-term use, pamidronate is still classified as not damaging to tissue.

However, *Marker et al.* reported on **11 dogs** with pamidronate extravasation. These developed swelling and redness at the injection site and tenderness or lameness of the affected leg. Two of the dogs also developed superinfection. The treatment of extravasation varied. Mainly **cold or warm compresses** and antibiotics were used and two dogs required debridement. One dog had to be euthanised due to extravasation. Pamidronic acid was therefore described by the authors as a tissue irritant in dogs.[67]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Swelling, redness, pain, localised warm sensation, induration and phlebitis at the injection site.

Reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis) are described as **differential diagnoses** for pamidronic acid.[85]

Pemetrexed (Pemetrexed medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measeures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: Initially 20-30 minutes, then as needed[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours.[59]
- *Perez Fidalgo et al.*: Application of dry cold, not further specified[90]

To date, there are **few reports** of extravasation for pemetrexed and these have not been considered serious by those reporting. Extravasations of pemetrexed should be treated with the usual standard local measures for extravasations of other non-tissue-damaging medicinal products.[89]

No cases of extravasation are available from medac's internal **spontaneous reporting system.**

Recall phenomena after radiotherapy are described as a **differential diagnosis.** In affected patients, the radiotherapy had already taken place weeks or years ago.[89]

Topotecan (Topotecan medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial management: yes (⇒ page 46)

Specific measeures: none[9,64]

Additional information:

Various authors recommend the use of **dry cold**:

- *Boulanger et al.*: 20-30 minutes, 4 times a day for 24-48 hours[21]
- *Kimmel et al.*: 15-20 minutes at least 4 times a day for the first 24 hours[59]

Extravasations are very rare and the reported reactions were mild and generally did not require specific therapy.[101]

Two patients have been reported in the **literature** to have developed mild pain following extravasation of topotecan due to swelling/tissue expansion in the area of extravasation. In both cases, this swelling was absorbed within 24 hours and no serious complications occurred. In one of the two cases, the affected area was cooled.[83]

The following symptoms were reported from medac´s internal **spontaneous reporting system**: Swelling, pain and redness.

So far, no **differential diagnoses** of extravasation with topotecan have been described.

Treosulfan (Ovastat®, Trecondi®)

Risk of tissue damage: moderate

Type of tissue damage: irritation[42]

Initial management: yes (⇒ page 46)

Specific measures: none[9,64]

Additional information:

So far, no substance-specific measures can be recommended.[64]

Extravasations with treosulfan may cause painful inflammatory reactions of the tissue.[84]

Treosulfan is also classified as a necrotising agent due to the formation of methanesulfonic acid released during degradation. However, no reports of necrosis are known.[10] Therefore, treosulfan is classified as a tissue irritant. The skin irritation is probably caused by the acidic pH of the reconstituted solution of 3.5.[64]

No cases of extravasation have been described in the **literature** so far.

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Swelling, redness, pain, skin discolouration, skin desquamation, blistering, ulceration and wound formation. In these cases, the following measures were successfully applied: Cooling, subcutaneous/topical or oral cortisone, subcutaneous heparin, subcutaneous sodium chloride, subcutaneous scandicaine, DMSO.

So far, no **differential diagnoses** of extravasation with treosulfan have been described.

Vinorelbine (Navirel®)

Risk of tissue damage:	high
Type of tissue damage:	necrosis
Initial management:	yes (⇒ page 46)
Specific measures:	**flushing** of the affected vein with saline solution (0.9 %)[80] subcutaneous or intradermal perilesional injections with **hyaluronidase** (off-label use) dosage: 1-10 ampoules of 150 IU (depending on the size of the affected area) under adequate analgesia [9, 64] *AND* **dry heat**, 4 times a day for 20 min for 24-48 hours.[9, 32]

Additional information:

Dry cold application is not recommended for vinorelbine.[9]

For further information on therapy with **hyaluronidase**, please refer to the corresponding section under SPECIFIC MEASURES .

If vinorelbine infiltrates the surrounding tissue during intravenous use, significant local irritation may occur.[80]

In case of incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy, involve **surgeons** [9]

The use of glucocorticoids in extravasations with vinorelbine is controversially discussed in the **literature**. In individual cases, therapeutic success has been reported in patients.[22,77]
In mice, however, it was reported by *Dorr et al.* that local application of hydrocortisone and cooling increases the toxicity of vinca alkaloids and is therefore contraindicated.[35]
As extravasation is rarely accompanied by an inflammatory response, systemic and topical steroids are not currently recommended.[9,64]

Gonzales reports a case of erythema and severe pain after extravasation. After cooling and administration of painkillers and silver sulphadiazine cream, complete healing occurred.[45]
Furthermore, *Das et al.* report a case of ulceration and blistering 4 days after vinorelbine extravasation from a port. After administration of antibiotics, 900 IU hyaluronidase s.c. and heat, the lesion regressed with scarring.[30]
Other cases of blistering even without preceding pain or swelling have been reported.[50, 65]
Bertelli et al. reported a case series of a patient in whom the use of hyaluronidase still resulted in successful treatment with vinorelbine 10 days after peripheral extravasation had occurred.[14]

The following symptoms have been reported in cases from medac´s internal **spontaneous reporting system**: Pain, burning sensation, redness, skin desquamation, induration, blistering, tingling, phlebitis, recall phenomenon, haematoma, scarring and ulceration.

Differential diagnoses include injection site reactions such as redness, burning pain, venous discolouration and local phlebitis (G3-4: 3.7% with vinorelbine as sole chemotherapeutic agent) in > 10% of all cases. Necrosis at the injection site occurs rarely.[80]

Zoledronic acid (Zoledronic acid medac)

Risk of tissue damage: low

Type of tissue damage: no tissue damage

Initial managment: yes (⇒ page 46)

Specific measures: none

Additional information:

No substance-specific measures can be recommended; bisphosponates are not described in the current guidelines for the treatment of extravasation.

Cases of extravasation have not been described in the **literature** so far.

The following symptoms have been reported in cases from medac's internal **spontaneous reporting system**: Swelling, overheating of the skin.

Differential diagnoses described for zoledronic acid are infusion site reactions (including pain, irritation, swelling, induration).[111]

INITIAL MANAGEMENT

(As per[9,32,64,109])

Extravasation with peripheral venous access

1. If extravasation is suspected, **stop** injection/infusion **immediately.**
   Do not remove the cannula
2. Put on (sterile) gloves, then **aspirate** the extravasate through the horizontal cannula and remove the cannula under aspiration
3. Do not apply pressure to the extravasation site
4. For tissue-irritating/necrotising cytostatic drugs: In case of blisters or large extravasation, these should be aspirated from all sides with a suitable cannula
5. **Elevate** and **immobilise** the affected limb
6. Initiate adequate **analgesia** (if required)
7. Initiate substance-specific **measures** (dry cold or heat, antidote if applicable)
8. NO moist or alcohol poultices, NO occlusive dressings
9. **Document** the incident exactly (photo, documentation protocol, if necessary mark the affected area with waterproof felt pen for size progression)
10. **Advise** patients and relatives about extravasation symptoms and consequences, advise self-observation (pain, swelling, redness)
11. Consultate a **surgeon** (in case of necrotising substances, incipient necrosis, incipient compartment syndrome, persistent/progressive pain or failure of conservative therapy)
12. Regular **follow-up** and documentation depending on the necrotising potential of the substance and observed symptoms until the acute local reaction has subsided (e.g. for necrotising substances every 8 h during the first 24 h)

Extravasation with port system / central venous catheter

1. If extravasation is suspected, **stop** injection/infusion **immediately**
   Leave central catheter or port needle in place
2. Put on (sterile) gloves, then **aspirate** as much as possible with a 10 ml syringe
3. Do not apply pressure to the extravasation site
4. Initiate adequate **analgesia** (if required)
5. Initiate substance-specific **measures** (dry cold or heat, antidote if applicable), do not apply antidote via the central line
6. Remove port needle/central venous catheter under aspiration
7. Consult **surgeon** immediately (imaging, drainage if necessary, thoracoscopy/-tomy)
8. Ensure adequate **analgesia, volume and oxygen administration** (if necessary)
9. Anti-infective therapy (if necessary)
10. **Document** the incident exactly (photo, extravasation protocol, marking of the extravasation site if necessary)
11. **Advise** patients and relatives about extravasation symptoms and consequences, encourage self-observation
12. Regular **follow-up** and documentation depending on the damage potential of the substance and symptoms

ADDITIONAL MEASURES

Consider antibiotic prophylaxis (e.g. clindamycin or amoxicillin) and hospital admission for widespread extravasations with large substance defects or for patients at risk.[9,90]

SPECIFIC MEASURES

Dry cold

Important:

Dry cold (e.g. cold compresses) - moist cold macerates the skin[64]

Never apply cold compresses directly on the skin

Do not use with vinca alkaloids[9]

Do not use with oxaliplatin[32,64]

Effect:

Vasoconstriction with slowing down of diffusion and decreased elimination, local containment of the extravasated drug[13,34]

Decrease of cellular absorption of doxorubin *in vitro*[48,64]

Decrease of cytotoxic effect of doxorubin in mice[48]

Advantages:

Easy to carry out

Non-invasive

Synergistic effect with DMSO[15]

Disadvantages:

Increase of toxicity of vinca alkaloids in mice[35]

Limited efficacy as a stand-alone measure[48,64]

Application:

For further information on dry cold therapy, please refer to the respective substance-specific sections.

Used in combination with DMSO for[9,32,64]

- Doxorubicin
- Epirubicin
- Mitomycin

Dry heat

Important: Dry heat (e.g. heat compresses) - moist heat macerates the skin and promotes necrosis[64]

Never apply heat compresses directly on the skin

Effect: Vasodilatation with increase in local blood circulation and faster elimination, thereby lowering the local cytostatic concentration[9,64]

Advantages: Easy to carry out

Non-invasive

Disadvantages: Increases the residual activity of some cytostatic drugs, e.g. doxorubicin (*in vitro* and in mice), therefore risk of increased tissue damage [64]

Other: Synergistic effect with hyaluronidase for vinca alkaloids hypothesised[64]

Application: For further information on dry heat therapy, please refer to the respective substance specific sections.

Used in combination with hyaluronidase for[9,32,64]

- Vinorelbin (vinca alkaloids)

Dexrazoxane (Savene®)

Important:

Has to be given within 6 h after anthracycline extravasation occurs, infusion duration 1-2 hours. No simultaneous DMSO application
In the case of simultaneous mitomycin or vinca alkaloid extravasation, dexrazoxane has no effect against the reactions of these compounds
If the extravasated area is also cooled, this must be stopped at least 15 minutes before administration to ensure adequate blood flow
Caution in patients with hepatic, renal dysfunction and patients on potassium- or sodium-controlled diets
♂ and ♀ must use safe contraception during therapy and must not conceive or become pregnant for up to 6 months after the end of therapy
Storage after reconstitution at 2-8°C for a maximum of 4 hours[96]

Effect:

Chelation of iron
Inhibition of topoisomerase II

Advantages:

Approved medicinal product against anthracycline extravasation with clinically proven efficacy [96]

Disadvantages:

Has to be administered systemically
May cause potentially serious side effects
May increase toxicity of chemotherapy (especially haematological toxicity)[96]
Very high treatment costs[92]

Other:

Dexrazoxane itself is a cytostatic drug
Dexrazoxane has been used since the 1990s for the prophylaxis of anthracycline-induced cardiomyopathy (Cardioxane®)[25]

Administration:

Reconstitute before use according to the product information
Treatment once daily for 3 consecutive days:

- Day 1: 1000 mg/m²,
- Day 2: 1000 mg/m²,
- Day 3: 500 mg/m²

Single doses must not exceed 2000 mg, dose reduction in case of renal dysfunction, see product information
Always give the infusion at the same time (+/- 3 h)
Intravenous infusion over 1-2 h via a large vein in a limb not affected by extravasation[96]
In the case of very small extravasations and lack of clinical symptoms, the application can be foregone[9]

For further information on therapy with dexrazoxane, please refer to the respective substance-specific sections.

Used for anthracyclines[96]

- Doxorubicin
- Epirubicin

Dimethyl sulfoxide (DMSO)

Important:
Ensure sufficient concentration, 99% is recommended
No simultaneous use with dexrazoxane
In case of extravasation of liposomal anthracyclines, the application is contraindicated[9]

Effect:
Anti-inflammatory, local anaesthetic, vasodilator, collagen dissolving [10]
Rapid tissue penetration and exceptional solvent properties (aids tissue penetration)[64]
Potent free radical scavenger, useful for free radical forming drugs such as anthracyclines [64]

Advantages:
Easy to carry out
Non-invasive
Well tolerated[64]
Efficacy well documented[64]

Disadvantages:
Characteristic garlic-like halitosis and garlic-like taste (up to 3 days after therapy)
Concentration-dependent reversible skin reactions (e.g. burning, pruritus, erythema, urticaria, blistering, drying out and desquamation of the skin)

Other:
In combination with intermittent cooling, a very effective antidote for tissue-necrotising substances such as anthracyclines

Application:
Immediately (within 10 - 25 minutes) 3 x daily (more often if necessary with mitomycin[74]) 4 drops per 10 cm^2 99% DMSO solution sterilely (do not rub) and let it air dry - do not cover
In combination with dry cold, keep a time interval of at least 15 minutes[9]

For further information on therapy with DMSO, please refer to the respective substance-specific sections.

Used in combination with cold for[9,32,64]

- Doxorubicin (if dexrazoxane was not used)
- Epirubicin (if dexrazoxane was not used)
- Mitomycin

Hyaluronidase

Important: Ensure sufficiently high dose[32], up to 1.500 I.U. is recommended[9]
Perilesional injection, i.e. around the extravasation area
Off-label use

Effect: Enzymatic degradation of hyaluronic acid as well as chondroitic acid and mucoitin sulphates, thereby structural loosening of connective and supporting tissues and increased absorption of extravasate from the affected site[64]

Advantage: Minor side effects[64]

Disadvantage: Invasive procedure
Injection associated with severe, burning pain[64]

Other: Synergistic effect with heat discussed for vinca alkaloids[64]

Application: Perilesional, subcutaneous or intradermal injection of the affected area with 1-10 ampoules (150 I.U. each) up to 1,500 I.U (like the dial of a watch)[9,64]
Solution of hyaluronidase in 1 ml solvent (e.g. 0.9 % saline solution)
Use appropriate analgesia (local anaesthesia, e.g. lidocaine 1 % and oral analgesics if necessary)[9,32]

Used for[9,32,64]

- Paclitaxel

Used in combination with dry heat for[9,32,64]

- Vinorelbine

Non-recommended measures

Sodium bicarbonate (sodium hydrogen carbonate)

Important: Due to the risk of necrosis from sodium bicarbonate itself, use is **not** recommended.[64]

Sodium thiosulfate

Important: Use is **not** recommended.

The efficacy of sodium thiosulphate is not sufficiently proven clinically. It is also an invasive measure that can be circumvented by the use of DMSO. The application of DMSO can lead to an equivalent therapeutic success[9,64].

Steroids

Important: The use of systemic or topical steroids is **not** recommended from a pharmacological point of view, as extravasations are only accompanied by inflammatory processes in rare cases.[9,64]

Surgical interventions

Surgical interventions may include extensive debridement with secondary plastic coverage or the so-called "SWOP" (saline/subcutaneous washout procedure) technique and should only be performed by appropriately experienced staff.[9]

A (plastic) surgeon should be consulted in the following situations, among others:[9,64]

- Extensive or severe extravasation where damage to e.g. tendons, nerves etc. is expected, port extravasation
- Persistent local pain or failure of conservative therapy
- Ulceration or scarring
- Impending compartment syndrome
- Incipient necrosis
- For tissue-necrotising substances depending on the amount and location of the extravasation
- Moist necrosis with risk of superinfection

Pluschnig et al. showed in a study that indocyanine green angiography is suitable for predicting the extent of tissue damage in peripheral venous extravasations with strongly irritating and necrotising substances. A good perfusion of the affected area, which could be visualised on imaging, was shown to be a good indicator of the extent of tissue damage and therefore of the success of healing with conservative management. The method was suitable to identify patients who are candidates for surgical intervention.[92]

THE EXTRAVASATION SET

(As per[9,64])

The set

Materials

- Disposable syringes (1 ml, 2 ml, 5 ml, 10 ml and 20 ml)
- Sterile cannula (s.c., i.v.)
- Peripheral venous access catheters
- Gloves, unsterile and sterile, different sizes
- Skin-friendly fixation plasters
- Cold-Hot-Pack
  at least 2 pieces for warmth
  at least 2 pieces for cooling ➔ **keep at 2 - 8°C**
- Sterile compresses and swabs

Drugs and fluids

- Destilled water
- Isotonic saline 0.9%, 10 x 10 ml
- Glucose 5% (for oxaliplatin extravasation, in case flushing is indicated use glucose 5% and not saline)
- Local anaesthetic,e.g. lidocaine 1%
- Dexrazoxane (Savene®10 vials with 500 mg Savene® powder and 3 bags with 500 ml Savene®-Diluent), alternatively reference for dexrazoxane availability (city/location, phone number)
- Dimethyl sulfoxide (DMSO) Ph.Eur. 99% – 2 x 100 ml
- Hyaluronidase 1.500 I.U. ➔ **keep at 2 - 8°C**

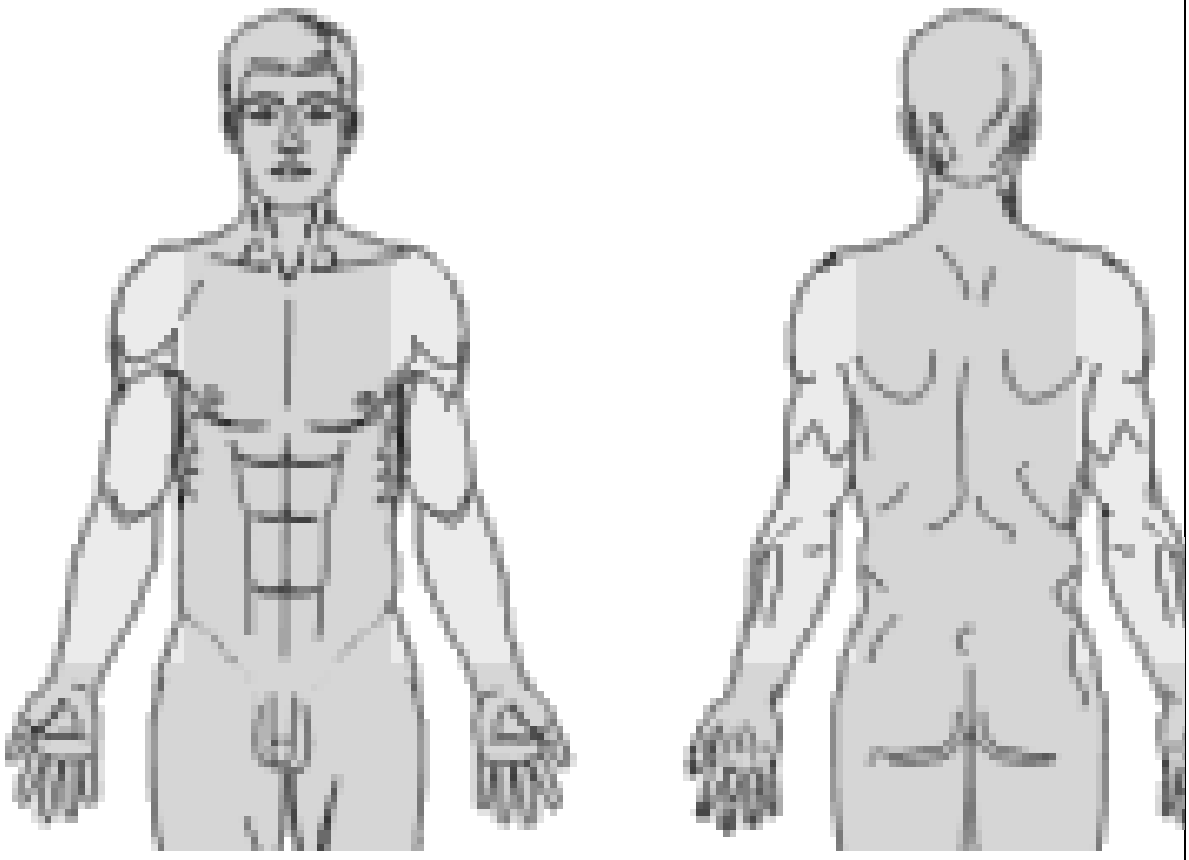
Overviews and documentation

- Overview of drugs and their damage potential
- Overview of initial management, additional and specific measures
- Measuring tape and water proof felt pen
- Documentation form for suspected extravasations
- Monitoring sheet
- Reporting form

Documentation form

(for suspected extravasations)

Patient	
Patient	
Name	
Date of birth	
Address	
Height/weight	
Body surface (m^2)	
Date and time of the extravasation	
Cytotoxic drug	
Drug name	
Suspected volume of extravasation	
Concentration	
Sequence	
Access	
Type/localisation of access	
Needle type and -size	
Central venous catheter?	
Pump / perfusion pump (Model)	
Flow rate	
Symptoms	
Subjective symptoms of the patient	
Visible changes	
Size of the affected area	
Initial management	
Date/time of first intervention	
General measures (elevation, immobilisation etc.)	
Special measures	
Cold	
Heat	
DMSO=Dimethyl sulfoxide	
Hyaluronidas	
Dexrazoxane	
Further measures	
Marking of the affected area (water proof felt pen)	
Photo documentation	
Patient information	
Further interventions	
Comments:	

Mark localisation and size of skin changes	
	
Date / Signature (Physician)	

Monitoring sheet

Coding (see following coding scale)

Control intervals depend on the damage potential of the extravasated substance and the clinical extent of extravasation[9].

	Status after extravasation	1st control	2nd control	3rd control	4th control	5th control	6th control
Date							
V=visit							
P=phone							
Size of affected area (cm x cm)							
Colour of skin (0-4)							
Skin characteristics (0-4)							
Temperature of the skin (0-2)							
Oedema (0-2)							
Mobility (0-3)							
Pain (0-3)							
Fever (°C)							
Others							
Date / signature							

Coding scale					
Grade	0	1	2	3	4
Colour of skin	normal	reddish	red	pale centre, surrounded by a red ring	darkish
Skin characteristics	normal	blisters	superficial skin damage	tissue damage	deep tissue damage
Temperature of skin	normal	warm	hot		
Oedema	-	+	++ (indentations)		
Mobility	complete	slightly limited	limited	immobile	
Pain	no	slight	moderate	severe	

Outcome	
Date of assessment	
Complete recovery	Yes / No
Scarring	Yes / No
Ulceration	Yes / No
Restriction of mobility	Yes / No
Follow-up planned (when)?	
Surgical interventions (Which? e.g. skin grafting)	
Other	

Reporting form

Extravasation Documentation Form	**Report to:** medac GmbH Pharmacovigilance Theaterstraße 6 **fax: +49 (0) 4103 / 8006-9130** D-22880 Wedel phone: +49 (0) 4103 / 8006-777 Germany **e-mail: drugsafety@medac.de**

I. Patient data

Patient's initials	Date of birth	Patient's sex	
_____ first- surname	Day Month Year	☐ male ☐ female	height: ____ cm weight: ____ kg

Basic disease:	medac reference number

Extravasation recognised: Day Month Year

II. Symptoms after extravasation

Short description (symptoms, localisation, extent of extravasation)

III. Sequence of applicated drugs

Trade name / substance	Manufacturer and batch number	dosage / unit	planned type of administration	date of last administration	Estimated volume of extravasated drug (ml)
1.					
2.					
3.					

IV. Therapeutic measures

Aspiration of drug possible? ☐ yes ☐ no

Recommended general and substance specific measures taken? ☐ yes ☐ no

Additional measures taken:.....

Surgical measures:.....

Status after extravasation:

☐ Deterioration
☐ No change
☐ Improvement
☐ other:

.....

Reporter: ☐ Physician ☐ Pharmacist ☐ other :_____ Name: E-Mail: Phone: Date / Signature:	Stamp

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Arsenic trioxide medac 1 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: Each ml of concentrate contains 1 mg of arsenic trioxide. One vial of 10 ml contains 10 mg of arsenic trioxide. *Excipients:* Sodium hydroxide, hydrochloric acid, water for injections. **Therapeutic indications:** Arsenic trioxide medac is indicated for induction of remission, and consolidation in adult patients with: **-** Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA)**; -** Relapsed/refractory APL (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the pro-myelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RARα) gene. The response rate of other AML subtypes to arsenic trioxide has not been examined. **Posology and method of administration:** Newly diagnosed low-to-intermediate risk APL: *Induction*: Intravenously at a dose of 0.15 mg/kg/day, given daily until complete remission (CR) is achieved. If CR has not occurred by day 60, dosing must be discontinued. *Consolidation:* Intravenously at a dose of 0.15 mg/kg/day, 5 days per week. Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles. Relapsed/refractory APL: *Induction:* Intravenously at a fixed dose of 0.15 mg/kg/day given daily until CR is achieved (less than 5% blasts present in cellular bone marrow with no evidence of leukaemic cells). If CR has not occurred by day 50, dosing must be discontinued. *Consolidation:* Begin 3 to 4 weeks after completion of induction therapy; intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks. Arsenic trioxide medac must be administered intravenously over 1 2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. **Undesirable effects:** Related adverse reactions of CTC grade 3 and 4 occurred in 37 % of relapsed/refractory APL patients in clinical trials. The most commonly reported reactions were hyperglycaemia, hypokalaemia, neutropenia, and increased alanine amino transferase (ALT). Leucocytosis occurred in 50 % of patients with relapsed/refractory APL, as determined by haematology assessments. *Infections, infestations:* Commonly herpes zoster. Sepsis, pneumonia (frequency unknown). *Blood, lymphatic system:* Commonly febrile neutropenia, leucocytosis, neutropenia, pancytopenia, thrombocytopenia, anaemia. Leukopenia, lymphopenia (frequency unknown). *Metabolism, nutrition:* Very commonly hyperglycaemia, hypokalaemia, hypomagnesaemia. Commonly hypernatremia, ketoacidosis, hypermagnesemia. Dehydration, fluid retention (frequency unknown). *Psychiatric:* Confusional state (frequency unknown). *Nervous system:* Very commonly paraesthesia, dizziness, headache. Commonly convulsion. Encephalopathy, Wernicke encephalopathy (frequency unknown). *Eye:* Commonly vision blurred. *Cardiac:* Very commonly tachycardia. Commonly pericardial effusion, ventricular extrasystoles. Cardiac failure, ventricular tachycardia (frequency unknown). *Vascular:* Commonly vasculitis, hypotension. *Respiratory, thoracic, mediastinal:* Very commonly differentiation syndrome characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. Commonly hypoxia, pleural effusion, pleuritic pain, pulmonary alveolar hemorrhage. Pneumonitis (frequency unknown). *Gastrointestinal:* Very commonly diarrhoea, vomiting, nausea. Commonly abdominal pain. *Skin, subcutaneous tissue:* Very commonly pruritus, rash. Commonly erythema, face oedema. *Musculoskeletal, connective tissue:* Very commonly myalgia. Commonly arthralgia, bone pain. *Renal:* Commonly renal failure. *General, administration site:* Very commonly pyrexia, pain, fatigue, oedema. Commonly chest pain, chills. *Investigations:* Very commonly Alanine amino transferase or Aspartate amino transferase increased, electrocardiogram QT prolonged. Commonly hyperbilirubinemia, blood creatinine increased, weight increased. Gamma-glutamyltransferase increased (frequency unknown). *Additional selected adverse reactions:* Mortality from disseminated intravascular coagulation (DIC) associated haemorrhage; peripheral neuropathy, characterised by paraesthesia/dysesthesia; hepatotoxicity (grade 3-4). **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 04/2022

Arsenic trioxide medac has been authorised in all countries of the EU as well as in Iceland, Kazakhstan, Liechtenstein and Norway

Spectrila® 10,000 U powder for concentrate for solution for infusion

Qualitative and quantitative composition: Each vial contains 10,000 units of asparaginase produced in *Escherichia coli* cells by recombinant DNA technology. One unit (U) is defined as the quantity of enzyme required to liberate one µmol ammonia per minute at pH 7.3 and 37°C. After reconstitution each ml contains 2,500 units of asparaginase. *Excipient:* Sucrose. **Therapeutic indications:** As a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults. **Posology and method of administration:** Spectrila is usually employed as part of combination chemotherapy protocols with other antineoplastic agents. *Adults and children older than 1 year:* The recommended intravenous dose of asparaginase is 5,000 (U/m²) BSA given every third day. Treatment may be monitored based on the trough serum asparaginase activity measured three days after administration. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered. *Children 0– 12 months old:* Based on limited data, the recommended dose is: age less than 6 months 6,700 U/m² BSA; age 6– 12 months 7,500 U/m² BSA. For administration by intravenous infusion only. **Contraindications:** Hypersensitivity to the active substance, any native (non-pegylated) E. coli-asparaginase preparation or to the excipient; pancreatitis; severe hepatic impairment (bilirubin > 3 times ULN; transaminases > 10 times ULN); pre-existing known coagulopathy (e.g. haemophilia); history of pancreatitis, serious haemorrhage or serious thrombosis with prior asparaginase therapy. **Undesirable effects:** *Infections, infestations:* Infections (frequency not known). *Blood, lymphatic system:* Commonly disseminated intravascular coagulation (DIC), anaemia, leukopenia, thrombocytopenia. *Immune system:* Very commonly hypersensitivity including flushing, rash, hypotension, oedema/angioedema, urticaria, dyspnoea. Commonly hypersensitivity including bronchospasm. Rarely anaphylactic shock. *Endocrine:* Very rarely secondary hypothyroidism, hypoparathyroidism. *Metabolism, nutrition:* Very commonly hyperglycaemia, hypoalbuminaemia. Commonly hypoglycaemia, decreased appetite, weight loss. Uncommonly hyperuricaemia, hyperammonaemia. Rarely diabetic ketoacidosis. *Psychiatric:* Commonly depression, hallucination, confusion. *Nervous system:* Commonly neurological signs and symptoms including agitation, dizziness and somnolence. Uncommonly headaches. Rarely ischaemic stroke, reversible posterior leukoencephalopathy syndrome (RPLS), convulsion, disturbances in consciousness including coma. Very rarely tremor. *Vascular:* Commonly thrombosis especially cavernous sinus thrombosis or deep vein thrombosis, haemorrhage. *Gastrointestinal:* Very common diarrhoea, nausea, vomiting, abdominal pain. Commonly acute pancreatitis. Rarely haemorrhagic pancreatitis, necrotising pancreatitis, parotitis. Very rarely pancreatitis with fatal outcome, pancreatic pseudocyst. *Hepatobiliary:* Rarely hepatic failure with potentially fatal outcome, hepatic necrosis, cholestasis, jaundice. Hepatic steatosis (frequency not known). *General, administration site:* Very commonly oedema, fatigue. Commonly pain (back pain, joint pain). *Investigations:* Very commonly increase in transaminases, blood bilirubin, blood alkaline phosphatase, blood cholesterol, blood triglyceride, very low density lipoprotein (VLDL), lipoprotein lipase activity, blood urea, ammonia, blood lactate dehydrogenase (LDH), decrease in antithrombin III, blood fibrinogen, blood cholesterol, low density lipoprotein (LDL), total protein. Commonly increase in amylase, lipase, abnormal electroencephalogram (EEG) (reduced alpha wave activity, increased theta and delta wave activity). **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 03/2023

Spectrila has been authorised in all countries of the EU as well as in Iceland, Kazakhstan, Liechtenstein, Norway and United Kingdom

Bendamustine medac 2.5 mg powder for concentrate for solution for infusion

Qualitative and quantitative composition: 1 vial contains 25 mg (100 mg) bendamustine hydrochloride (as bendamustine hydrochloride monohydrate). 1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted. *Excipient:* Mannitol. **Therapeutic indications:** First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment. **Posology and method of administration:** *Monotherapy for chronic lymphocytic leukaemia:* 100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks, up to 6 times. *Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab:* 120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks, for at least 6 times. *Multiple myeloma:* 120 – 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4; every 4 weeks, for at least 3 times. Treatment should be terminated or delayed if leukocyte and/or platelet values have dropped to < 3,000/µl or < 75,000/µl, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/µl and platelet values to > 100,000/µl. During therapy free intervals strict monitoring of the blood count is recommended. For intravenous infusion over 30 – 60 minutes. **Contraindications:** Hypersensitivity to the active substance or excipient; breastfeeding; severe hepatic impairment (serum bilirubin > 3.0 mg/dl); jaundice; severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively); major surgery less than 30 days before start of treatment; infections, especially involving leukocytopenia; yellow fever vaccination. **Undesirable effects:** *Infections, infestations:* Very commonly infection, including opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B); uncommonly Pneumocystis jirovecii pneumonia; rarely sepsis; very rarely pneumonia primary atypical. *Neoplasms:* Commonly tumour lysis syndrome; uncommonly myelodysplastic syndrome, acute myeloid leukaemia. *Blood, lymphatic system:* Very commonly leukopenia, thrombocytopenia, lymphopenia; commonly haemorrhage, anaemia, neutropenia; uncommonly pancytopenia; rarely bone marrow failure; very rarely haemolysis. The CD4/CD8 ratio may be reduced; reduction of the lymphocyte count was seen; in immuno-suppressed patients risk of infection may be increased. *Immune system:* Commonly hypersensitivity; rarely anaphylactic or anaphylactoid reaction; very rarely anaphylactic shock. *Nervous system:* Very commonly headache; commonly insomnia, dizziness; rarely somnolence, aphonia; very rarely dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis. *Cardiac:* Commonly cardiac dysfunction, such as palpitations, angina pectoris, arrhythmia; uncommonly pericardial effusion, myocardial infarction, cardiac failure; very rarely tachycardia; atrial fibrillation (frequency not known). *Vascular:* Commonly hypotension, hypertension; rarely acute circulatory failure; very rarely phlebitis. *Respiratory, thoracic, mediastinal:* Commonly pulmonary dysfunction; very rarely pulmonary fibrosis; pneumonitis, pulmonary alveolar haemorrhage (frequency not known). *Gastrointestinal:* Very commonly nausea, vomiting; commonly diarrhoea, constipation, stomatitis; very rarely haemorrhagic oesophagitis, gastrointestinal haemorrhage. *Hepatobiliary:* Hepatic failure (frequency not known). *Skin, subcutaneous tissue:* Commonly alopecia, skin disorders, urticaria; rarely erythema, dermatitis, pruritus, macular-papular rash, hyperhidrosis; Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) (frequency not known). *Renal, urinary:* Renal failure, nephrogenic diabetes insipidus (frequency not known). *Reproductive system, breast:* Commonly amenorrhea; very rarely infertility. *General, administration site:* Very commonly mucosal inflammation, fatigue, pyrexia; commonly pain, chills, dehydration, anorexia; very rarely multi organ failure; isolated reports of necrosis after accidental extra-vascular administration. *Investigations:* Very commonly haemoglobin decrease, creatinine increase, urea increase; commonly AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, hypokalemia. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 05/2023

Bendamustine has been authorised in Denmark, Estonia, Finland, Germany, Iceland, Italy, Latvia, Lithuania, The Netherlands, Portugal and Sweden.

Bleomedac / Bleomycin medac 15000 IU (Ph. Eur.), powder for solution for injection

Qualitative and quantitative composition: One vial of 10 ml contains 15000 IU of bleomycin (as bleomycin sulphate). 1 mg of dry weight of the powder is equivalent to at least 1500 IU (Ph.Eur.). 1 U (USP) is equivalent to 1000 IU (Ph. Eur.) *Excipients:* None. **Therapeutic indications:** In combination with other cytostatic drugs and/or radiation therapy: Squamous cell carcinoma (SCC) of the head and neck, external genitalia and cervix; Hodgkin's lymphoma; Non-Hodgkin's lymphoma of intermediate and high malignancy in adults; testis carcinoma (seminoma and non-seminoma); intrapleural therapy of malignant pleural effusion. **Posology and method of administration:** *Warning:* Posology for all therapeutic indications is provided in IU and not in mg. Some protocols may state use "mg" instead of Units. This mg value refers to mg-activity and not to mg-dry material as these reflect different values. Bleomycin may be administered intravenously, intramuscularly, intrapleurally, intraperitoneally, intraarterially or subcutaneously. Local injection directly into the tumour may occasionally be indicated. Dose and intervals between injections are dependent on the indication, the method of administration, age and condition of the patient. The total dose of bleomycin in elderly patients should be reduced (see summary of product information). Administration of bleomycin in children should only take place in exceptional cases and in special centres. With impaired renal function, particularly with creatinine clearance < 35 ml/min, the elimination of bleomycin is delayed. **Contraindications:** Hypersensitivity to bleomycin; acute lung infection or severely reduced lung function; bleomycin-related lung toxicity or reduced lung function which can indicate bleomycin-related lung toxicity; ataxia telangiectasia; breast-feeding. **Undesirable effects:** Like most cytostatic drugs bleomycin can cause both an acute and a delayed toxic effect. Acute symptoms: anorexia, fatigue, nausea, fever. *Infections, infestations:* Infection, Sepsis (frequency not known). *Blood, lymphatic system:* Uncommonly bone marrow suppression, leukopenia, neutropenia, thrombocytopenia, haemorrhage. Rarely febrile neutropenia. Pancytopenia, anaemia (frequency not known). *Immune system:* Commonly hypersensitivity, idiosyncratic reaction, anaphylactic reaction. Anaphylactic reactions may be immediate or delayed for several hours, and usually occur after the first or second dose. It consists of hypotension, mental confusion, fever, chills, wheezing and can be fatal. *Metabolism, nutrition*: Very commonly decreased appetite. *Nervous system:* Paraesthesia, hyperaesthesia (frequency not known). *Cardiac:* Rarely myocardial infarction, coronary artery disease. *Vascular:* Rarely vascular injury, cerebral blood flow disorders, cerebral vasculitis, Haemolytic uraemic syndrome, arterial thrombosis. Hypotension, deep vein thrombosis, Raynaud's phenomenon (frequency not known). *Respiratory, thoracic, mediastinal:* Very commonly interstitial pneumonia, pulmonary fibrosis. Commonly acute respiratory distress syndrome, pulmonary embolism. Risk of pulmonary toxicity increases with the cumulative doses. Pulmonary toxicity can already occur with very low cumulative doses in elderly patients, patients who have received radiation of the thorax or who are receiving oxygen. Vascular changes occur in the lung, which partially affect the elasticity of the vessel wall. If unexplained coughing, dyspnoea, basal crepitations or a diffuse reticular image occurs on the X-ray of the thorax, any of these symptoms is a reason to discontinue the administration of bleomycin until the bleomycin toxicity has been ruled out as a cause. *Gastrointestinal:* Very commonly nausea, vomiting, mucosal inflammation, stomatitis, mucosal ulceration. Uncommonly diarrhoea. *Hepatobiliary:* Rarely hepatic impairment. *Skin, subcutaneous tissue:* Very commonly flagellate dermatitis, hyperpigmentation, skin hypertrophy, hyperkeratosis, erythema, rash, skin striae, blister, nail disorder, alopecia. Scleroderma (frequency not known). *Musculoskeletal, connective tissue:* Myalgia, pain in extremity, scleroderma (frequency not known). *Reproductive system:* Spermatozoa abnormal (frequency not known). *General, administration site:* Very commonly local swelling (fingertips and pressure susceptible places). Commonly pyrexia. Rarely hypotension, hyperpyrexia after intra-cavity administration. Very rarely tumour lysis syndrome. Injection site pain, infusion site thrombophlebitis (frequency not known). *Investigations:* Very commonly weight decreased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6, 22880 Wedel, Germany. **Date of revision of text**: 03/2023

Bleomedac / Bleomycin medac has been authorised in Czech Republic, Estonia, Germany, Latvia, Lithuania, The Netherlands, Poland, Slovak Republic and Slovenia

Bortezomib 1 mg /2.5 mg /3.5 mg powder for solution for injection

Qualitative and quantitative composition: Each vial contains 1 mg (2.5 mg; 3.5 mg) bortezomib (as a mannitol boronic ester). After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg Bortezomib (applies only to 2.5 and 3.5 mg); 1 ml of solution for intravenous injection contains 1 mg bortezomib. *Excipients:* Mannitol. **Therapeutic indications:** As monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. In combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. In combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. In combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation. **Posology and method of administration:** For monotherapie, Bortezomib 3.5 mg is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m² body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib. *Intravenous injection:* Bortezomib 3.5 mg reconstituted solution is administered as a 3 – 5-second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9 %) solution for injection. *Subcutaneous injection:* Bortezomib 3.5 mg reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45 – 90° angle. Injection sites should be rotated for successive injections. If local injection site reactions occur following Bortezomib subcutaneous injection, either a less concentrated Bortezomib solution (Bortezomib 3.5 mg to be reconstituted to 1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended. **Contraindications:** Hypersensitivity to the active substance, to boron or to any of the excipients, acute diffuse infiltrative pulmonary and pericardial disease. When bortezomib is given in combination with other medicinal products, refer to their SPCs for additional contraindications. **Undesirable effects:** *Infections, infestations:* Herpes zoster (inc disseminated & ophthalmic), pneumonia, herpes simplex, fungal, bacterial, viral infection, sepsis (inc septic shock), bronchopneumonia, Herpes virus infection, meningoencephalitis herpetic, Bacteraemia (inc staphylococcal), hordeolum, influenza, cellulitis, device related infection, skin or ear infection, Staphylococcal infection, tooth infection; meningitis (inc bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome. *Neoplasm:* Neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign. *Blood, lymphatic system:* Thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia, pancytopenia, febrile neutropenia, coagulopathy, leukocytosis, lymphadenopathy, haemolytic anaemia; disseminated intravascular coagulation, thrombocytosis, hyperviscosity syndrome, platelet disorder NOS, thrombotic microangiopathy (incl. thrombocytopenic purpura), blood disorder NOS, haemorrhagic diathesis, lymphocytic infiltration. *Immune system:* Angioedema, hypersensitivity; anaphylactic shock, amyloidosis, Type III immune complex mediated reaction. *Endocrine:* Cushing's syndrome, hyperthyroidism, inappropriate antidiuretic hormone secretion; hypothyroidism. *Metabolism, nutrition:* Decreased appetite; dehydration, hypokalaemia, hyponatraemia, blood glucose abnormal, hypocalcaemia, enzyme abnormality, tumour lysis syndrome, failure to thrive, hypomagnesaemia, hypophosphataemia, hyperkalaemia, hypercalcaemia, hypernatraemia, uric acid abnormal, diabetes mellitus, fluid retention; hypermagnesaemia, acidosis, electrolyte imbalance, fluid overload, hypochloraemia, hypovolaemia, hyperchloraemia, hyperphosphataemia, metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, gout, increased appetite, alcohol intolerance. *Psychiatric:* Mood disorders and disturbances, anxiety disorder, sleep disorders and disturbances; mental disorder, hallucination, psychotic disorder, confusion, restlessness; suicidal ideation, adjustment disorder, delirium, libido decreased. *Nervous system:* Neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia; motor neuropathy, loss of consciousness (inc syncope), dizziness, dysgeusia, lethargy, headache; tremor, peripheral sensorimotor neuropathy, dyskinesia, cerebellar coordination and balance disturbances, memory loss (exc dementia), encephalopathy, Posterior Reversible Encephalopathy Syndrome, neurotoxicity, seizure disorders, post herpetic neuralgia, speech disorder, restless legs syndrome, migraine, sciatica, disturbance in attention, reflexes abnormal, parosmia; cerebral haemorrhage, haemorrhage intracranial (inc subarachnoid), brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, autonomic neuropathy, cranial palsy, paralysis, paresis, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder NOS, motor dysfunction, nervous system disorder NOS, radiculitis, drooling, hypotonia, Guillain-Barré syndrome, demyelinating polyneuropathy. *Eye:* Eye swelling, vision abnormal, conjunctivitis; eye haemorrhage, eyelid infection, Chalazion, Blepharitis, eye inflammation, diplopia, dry eye, eye irritation, eye pain, lacrimation increased, eye discharge; corneal lesion, exophthalmos, retinitis, scotoma, eye disorder (inc. eyelid) NOS, dacryoadenitis acquired, photophobia, photopsia, optic neuropathy, different degrees of visual impairment (up to blindness). *Ear:* Vertigo, dysacusis (inc tinnitus), hearing impaired (up to and inc deafness), ear discomfort; ear haemorrhage, vestibular neuronitis, ear disorder NOS. *Cardiac:* Cardiac tamponade, cardio-pulmonary arrest, cardiac fibrillation (inc atrial), cardiac failure (inc left and right ventricular), arrhythmia, tachycardia, palpitations, angina pectoris, pericarditis (inc pericardial effusion), cardiomyopathy, ventricular dysfunction, bradycardia; atrial flutter, myocardial infarction, atrioventricular block, cardiovascular disorder (inc cardiogenic shock), torsade de pointes, angina unstable, cardiac valve disorders, coronary artery insufficiency, sinus arrest. *Vascular:* Hypotension, orthostatic hypotension, hypertension; cerebrovascular accident, deep vein thrombosis, haemorrhage, thrombophlebitis (inc superficial), circulatory collapse (inc hypovolaemic shock), phlebitis, flushing, haematoma (inc perirenal), poor peripheral circulation, vasculitis, hyperaemia (inc ocular); peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency. *Respiratory, thoracic and mediastinal:* Dyspnoea, epistaxis, upper/lower respiratory tract infection, cough; pulmonary embolism, pleural effusion, pulmonary oedema (inc acute), pulmonary alveolar haemorrhage, bronchospasm, chronic obstructive pulmonary

disease, hypoxaemia, respiratory tract congestion, hypoxia, pleurisy, hiccups, rhinorrhoea, dysphonia, wheezing; respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, haemoptysis, hyperventilation, orthopnoea, pneumonitis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial disorder, hypocapnia, interstitial lung disease, lung infiltration, throat tightness, dry throat, increased upper airway secretion, throat irritation, upper-airway cough syndrome. *Gastrointestinal:* Nausea and vomiting symptoms, diarrhoea, constipation; gastrointestinal haemorrhage (inc mucosal), dyspepsia, stomatitis, abdominal distension, oropharyngeal pain, abdominal pain (inc gastrointestinal and splenic pain), oral disorder, flatulence; pancreatitis (inc chronic), haematemesis, lip swelling, gastrointestinal obstruction (inc small intestinal obstruction, ileus), abdominal discomfort, oral ulceration, enteritis, gastritis, gingival bleeding, gastrooesophageal reflux disease, colitis (inc clostridium difficile), colitis ischaemic, gastrointestinal inflammation, dysphagia, irritable bowel syndrome, gastrointestinal disorder NOS, tongue coated, gastrointestinal motility disorder, salivary gland disorder; pancreatitis acute, peritonitis, tongue oedema, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma, gastrointestinal ulceration and perforation, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces. *Hepatobiliary:* Hepatic enzyme abnormality; hepatotoxicity (inc liver disorder), hepatitis, cholestasis; hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis. *Skin, subcutaneous tissue:* Rash, pruritus, erythema, dry skin; erythema multiforme, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis, Stevens-Johnson syndrome, dermatitis, hair disorder, petechiae, ecchymosis, skin lesion, purpura, skin mass, psoriasis, hyperhidrosis, night sweats, decubitus ulcer, acne, blister, pigmentation disorder; skin reaction, Jessner's lymphocytic infiltration, palmar-plantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction, seborrhoea, cold sweat, skin disorder NOS, erythrosis, skin ulcer, nail disorder. *Musculoskeletal, connective tissue:* Musculoskeletal pain; muscle spasms, pain in extremity, muscular weakness; muscle twitching, joint swelling, arthritis, joint stiffness, myopathies, sensation of heaviness; rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, pain in jaw, bone disorder, musculoskeletal and connective tissue infections and inflammations, synovial cyst. *Renal, urinary:* Renal impairment; renal failure acute or chronic, urinary tract infection, urinary tract signs and symptoms, haematuria, urinary retention, micturition disorder, proteinuria, azotaemia, oliguria, pollakisuria; bladder irritation. *Reproductive system:* Vaginal haemorrhage, genital pain, erectile dysfunction; testicular disorder, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration. *Congenital:* Aplasia, gastrointestinal malformation, ichthyosis. *General, administration site:* Pyrexia, fatigue, asthenia; oedema (inc peripheral), chills, pain, malaise; general physical health deterioration, face oedema, injection site reaction, mucosal disorder, chest pain, gait disturbance, feeling cold, extravasation, catheter related complication, change in thirst, chest discomfort, feeling of body temperature change, injection site pain; death (inc sudden), multi-organ failure, injection site haemorrhage, hernia (inc hiatus), impaired healing, inflammation, injection site phlebitis, tenderness, ulcer, irritability, non-cardiac chest pain, catheter site pain, sensation of foreign body. *Investigations:* Weight decreased; hyperbilirubinaemia, protein analyses abnormal, weight increased, blood test abnormal,C-reactive protein increased; blood gases abnormal, electrocardiogram abnormalities (inc QT prolongation), international normalised ratio abnormal, gastric pH decreased, platelet aggregation increased, troponin I increased, virus identification and serology, urine analysis abnormal. *Injury:* Fall, contusion; transfusion reaction, fractures, rigors, face injury, joint injury, burns, laceration, procedural pain, radiation injuries. Macrophage activation. **Legal classification:** POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text:** 11/2021

Bortezomib has been authorised in Finland, France, Germany, Italy, Poland, Sweden and United Kingdom (not all strengths are authorized in all countries)

Carbomedac® 10 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: Each ml contains 10 mg carboplatin. 1 vial of 5ml (15ml; 45ml; 60ml; 100ml) solution for infusion contains 50mg (150mg; 450mg; 600mg; 1000mg) of carboplatin. *Excipients:* Water for injections. **Therapeutic indications:** Alone or in combination with other antineoplastic medicinal products for the treatment of: advanced ovarian carcinoma of epithelial origin (first line therapy or second line therapy, after other treatments have failed); small-cell carcinoma of the lung. **Posology and method of administration:** Use by intravenous route only. The recommended dosage in previously untreated adult patients with normal kidney function is 400 mg/m² as a single dose administered by a 15 to 60 min. infusion. Alternative dosage by Calvert formula: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]. Target AUC is 5-7 mg/ml x min for monotherapy in previously untreated patients; 4-6 mg/ml x min for monotherapy in previously treated patients; 4-6 mg/ml x min for carboplatin plus cyclophosphamide in previously untreated patients. Therapy should not be repeated until four weeks after the previous course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³. Reduction of the initial dosage by 20-25% recommended for patients with risk factors such as prior myelosuppressive treatment and low performance status; creatinine clearance values < 60 ml/min are at greater risk of developing myelosuppression. In case of a GFR < 30 ml/min carboplatin should not be administered. *Paediatric population:* As no sufficient experience is available, no specific dosage recommendations can be given. *Elderly patients:* Dosage adjustment, initially or subsequently, may be necessary, dependent on physical condition. **Contraindications:** Hypersensitivity to carboplatin; pre-existing severe renal impairment (GFR < 30ml/min) unless in the judgement of physician and patient the possible benefits of treatment outweigh the risks; severe myelosuppression; bleeding tumours; concomitant use with yellow fever vaccine; patients with a history of severe allergic reaction to platinum-containing components; breast-feeding. **Undesirable effects:** *Infections, infestations:* Commonly infections (fatal in < 1%). Frequency not known: Pneumonia. *Neoplasms:* Very rarely acute promyelocytic leukaemia 6 years after monotherapy with carboplatin and previous radiotherapy. Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported. *Blood, lymphatic system:* Very commonly thrombocytopenia, neutropenia, leukopenia, anaemia. Myelosuppression is the dose-limiting toxicity of carboplatin injection. It is more severe in previously treated patients and patients with poor performance status (complications fatal in < 1%). Commonly haemorrhage (fatal in < 1%). Rarely febrile neutropenia, sepsis/septic shock. Frequency not known: Haemolytic anaemia (including fatal outcomes), bone marrow failure, haemolytic-uraemic syndrome. *Immune system:* Commonly hypersensitivity (e.g. skin rash, urticaria, erythema, fever with no apparent cause or pruritus), anaphylactoid type reaction (angiooedema, facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm), sometimes fatal. *Metabolism, nutrition:* Frequency not known: Dehydration, anorexia, hyponatraemia, tumour lysis syndrome. *Nervous system:* Commonly neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia. Uncommonly central nervous symptoms (often associated with antiemetics). Frequency not known: Cerebrovascular accident (fatal in < 1%), Reversible Posterior Leukoencephalopathy Syndrome, encephalopathy. *Eye:* Commonly visual disturbance; rarely loss of vision. Frequency not known: Optic neuritis. *Ear:* Commonly ototoxicity. Auditory defects out of the speech range with impairments in the high-frequency range (4,000-8,000 Hz) were found in serial audiometric investigations with a frequency of 15%. Very rare cases of hypoacusia. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients with a hearing organ predamaged due to cisplatin, further exacerbation sometimes occurs during treatment with carboplatin. At higher than recommended doses in combination with other ototoxic agents, clinically significant hearing loss has been reported to occur in paediatric patients. *Cardiac:* Commonly cardiovascular disorder (fatal in < 1%). Frequency not known: Cardiac failure (fatal in < 1%), ischaemic coronary heart diseases (e.g. myocardial infarction, cardiac arrest, angina pectoris, myocardial ischaemia), Kounis syndrome. *Vascular:* Frequency not known: Embolism (fatal in < 1%), hypertension, hypotension. *Respiratory:* Commonly respiratory disorder, interstitial lung disease, bronchospasm. *Gastrointestinal:* Very commonly vomiting, nausea, abdominal pain. Commonly diarrhoea, constipation, mucous membrane disorder. Frequency not known: Stomatitis, pancreatitis. *Hepatobiliary:* Frequency not known: Severe hepatic dysfunction (including acute liver necrosis). Modification of liver function in patients with normal baseline values was observed. *Skin, subcutaneous tissue:* Commonly alopecia, skin disorder. Rarely exfoliative dermatitis. Frequency not known: Urticaria, rash, erythema, pruritus. *Musculoskeletal, connective tissue:* Commonly musculoskeletal disorders. Uncommonly myalgia, arthralgia. *Renal and urinary:* Very commonly renal impairment. Commonly urogenital disorders, hyperuricaemia. *General, administration site:* Commonly asthenia. Uncommonly fever and chills without evidence of infection. Frequency not known: Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise. *Investigations:* Very commonly creatinine renal clearance decreased; blood urea, blood alkaline phosphatase, aspartate aminotransferase increased; liver function test abnormal; blood sodium, blood potassium, blood calcium, blood magnesium decreased. Commonly blood bilirubin, blood creatinine, blood uric acid increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 06/2023

Carbomedac® has been authorised in Denmark, France, Germany, Italy, Kazakhstan, Norway, Poland, Slovak Republic, Slovenia, Sweden and Ukraine

Dacarbazine medac 100mg (200mg), Powder for solution for injection / infusion; Dacarbazine medac 500mg (1000mg), Powder for solution for infusion

Each single-dose vial of Dacarbazine medac 100mg (200mg; 500mg; 1000mg) contains 100mg (200mg, 500mg, 1000mg) dacarbazine (as dacarbazine citrate, formed in situ). After reconstitution Dacarbazine medac 100mg (200mg) contains 10 mg/ml dacarbazine. After reconstitution and final dilution Dacarbazine medac 500mg (1000mg) contains 1.4–2.0 mg/ml (2.8–4.0 mg/ml) dacarbazine. *Excipients:* Citric acid, anhydrous; mannitol. **Therapeutic indications:** Treatment of patients with metastasized malignant melanoma. As part of combination chemotherapy: advanced Hodgkin's disease, advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma). **Dosage and method of use:** Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light also during administration. Avoid extravasation into tissues since this will cause local pain and tissue damage! If extravasation occurs, the injection should be discontinued immediately, and any remaining portion should be introduced into another vein. Malignant Melanoma: 200 to 250 mg/m² body surface area/day as an i.v. injection (or alternatively short-term infusion over 15 - 30 minutes) for 5 days every 3 weeks or 850 – 1000 mg/m² body surface area on day 1 and then once every 3 weeks as i.v. infusion. Hodgkin's disease: 375 mg/m² body surface area i.v. every 15 days in combination with doxorubicin, bleomycin and vinblastine (ABVD regimen). Adult soft-tissue sarcoma: 250 mg/m² body surface area i.v. (days 1-5) in combination with doxorubicin every 3 weeks (ADIC regimen). During dacarbazine treatment frequent monitoring of blood counts, monitoring of hepatic and renal function should be conducted. Antiemetic and supportive measures are advisable. A careful benefit-risk analysis has to be made before every course of therapy with dacarbazine. **Contraindications:** Hypersensitivity to dacarbazine or to any of the excipients; pregnancy or breastfeeding; leukopenia and/or thrombocytopenia; severe liver or kidney diseases; concomitant yellow fever vaccination or concomitant use of fotemustine. **Undesirable effects:** The most commonly reported ADRs are gastrointestinal disorders (anorexia, nausea and vomiting) and blood and lymphatic system disorders as anaemia, leucopenia and thrombocytopenia. The latter are dose-dependant and delayed, with the nadirs often only occurring after 3 to 4 weeks. *Infections, infestations:* Uncommonly infections. *Blood and lymphatic system:* Commonly anaemia, leucopenia, thrombocytopenia. Rarely pancytopenia, agranulocytosis. *Immune system:* Rarely anaphylactic reactions. *Nervous system:* Rarely headaches, impaired vision, confusion, lethargy, convulsions, facial paraesthesia. *Vascular:* Rarely facial flushing. *Gastrointestinal:* Commonly anorexia, nausea, vomiting. Rarely diarrhea. *Hepatobiliary:* Rarely hepatic necrosis due to veno-occlusive disease of the liver, Budd-Chiari syndrome (with potentially fatal outcome). Liver necrosis has been observed after administration of dacarbazine in monotherapy or in combined treatment modalities. In general the syndrome occurred during the second cycle of therapy. Symptoms included fever, eosinophilia, abdominal pain, enlarged liver, jaundice and shock which worsened rapidly over a few hours or days. *Renal, urinary:* Rarely impaired renal function. *Skin, subcutaneous tissue:* Uncommonly alopecia, hyperpigmentation, photosensitivity. Rarely erythema, maculopapular exanthema, urticaria. *General, administration site:* Uncommonly flu-like symptoms with exhaustion, chills, fever and muscular pain are occasionally observed during or often only days after dacarbazine administration. These disturbances may recur with the next infusion. Rarely application site irritation. Inadvertent paravenous injection is expected to cause local pain and necrosis. *Investigations:* Rarely hepatic enzymes increased (e.g. alkaline phosphatase, ASAT, ALAT), blood lactate dehydrogenase (LDH) increased, blood creatinine increased, blood urea increased. **Legal classification:** POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text** 08/2023

Dacarbazine medac has been authorized in Austria, Belgium, Colombia, Czech Republic, Denmark, Egypt, Finland, France, Germany, Israel (Tzamal Bio-Pharma), Jordan, Kazakhstan, The Netherlands, Portugal, Russia, Serbia (Quatalia), Slovak Republic, Spain, Sweden, Thailand, Ukraine and United Kingdom

Doxorubicin medac / Doxorubicin hydrochloride 2 mg/ml solution for infusion

Qualitative and quantitative composition: 1 ml contains 2 mg Doxorubicin hydrochloride. Each 5 ml (10 ml; 25 ml; 75 ml; 100 ml) vial contains a total content of Doxorubicin hydrochloride of 10 mg (20 mg; 50 mg; 150 mg; 200 mg). *Excipients:* Water for injections, sodium chloride, hydrochloric acid. **Therapeutic indications:** Small-cell lung cancer, breast cancer, recurrent ovarian carcinoma, systemic treatment of local advanced or metastasized bladder carcinoma, intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection, neoadjuvant and adjuvant therapy of osteosarcoma, advanced soft-tissue sarcoma in adults, Ewing's sarcoma, Hodgkin's disease, Non-Hodgkin's lymphoma, acute lymphatic leukaemia, acute myeloblastic leukaemia, advanced multiple myeloma, advanced or recurrent endometrial carcinoma, Wilms' tumour, advanced papillary/follicular thyroid cancer, anaplastic thyroid cancer, advanced neuroblastoma. Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic drugs. **Posology and method of administration:** Due to the risk of a lethal cardiomyopathy, the risks and benefits to the individual patient should be weighted before each application. Intravenous administration: To avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550 mg/m² body surface area. For patients with concomitant heart disease who received mediastinal and/or heart irradiation, prior treatment with alkylating agents or concomitant treatment with potentially cardiotoxic agents, and for high-risk patients maximum total dose of 400 mg/m² body surface area should not be exceeded and the cardiac function should be monitored. A dose of 60-75 mg/m² body surface area is recommended every three weeks when doxorubicin is used alone. In combination with other antitumor agents the dosage should be reduced to 30-40 mg/m² every three weeks. In patients who cannot receive the full dose an alternative dosage is 15-20 mg/m² per week. *Children:* Dosage should be reduced, since they have an increased risk for cardiac toxicity especially late toxicity. The maximal cumulative dose is 300 mg/m² (<12 years) and 450 mg/m² (>12 years). Intravesical use: The recommended dose for intravesical treatment of superficial cancer of the bladder is 30-50 mg in 25-50 ml of physiological saline per instillation. The optimal concentration is about 1 mg/ml. The solution should remain in the bladder for 1-2 hours. **Contraindications:** Hypersensitivity to the active substance, to any of the excipients or to other anthracyclines or anthracenediones. Dosage should not be repeated in the presence or development of bone marrow depression or buccal ulceration (preceded by premonitory buccal burning sensations). Intravenous administration: Persistent myelosuppression or severe stomatitis which appeared during previous cytotoxic treatment and/or radiation; general infection; severe hepatic impairment; known cardiac disorder (unstable angina pectoris, progressive heart failure, severe cardiac arrhythmias and conduction abnormalities, acute inflammatory heart disease, myocardial infarction during the past 6 months, myocardiopathy); previous treatment with anthracyclines with maximum cumulative doses; increased haemorrhagic tendency; breast-feeding. Intravesical administration: Invasive tumours that have penetrated the bladder (beyond T1); urinary tract infections**;** inflammation of the bladder; problems with catheterization e.g. urethral stenosis; haematuria; breast-feeding. **Undesirable effects:** *Infections, infestations:* Very commonly infection. Commonly sepsis, septicaemia. Uncommonly septic shock. *Neoplasms:* Uncommonly secondary acute myeloid leukaemia when given in combination with anti-neoplastic drugs which damage the DNA, acute lymphocytic leukaemia. *Blood, lymphatic system:* Very commonly myelosuppression, leukopenia, neutropenia, anaemia, thrombocytopenia, tissue hypoxia or death, febrile neutropenia. *Immune system:* Rarely anaphylactic reactions. *Metabolism, nutrition:* Commonly anorexia. Uncommonly dehydration. Rarely tumour lysis syndrome. Very rarely hyperuricaemia. *Eye:* Commonly conjunctivitis. Rarely lacrimation. Keratitis (frequency not known). *Cardiac:* Commonly cardiotoxicity, i.e. cardiomyopathy (2 %; e.g. decrease of LVEF, dyspnoea); sinus tachycardia, congestive heart failure, tachyarrhythmia, ventricular tachycardia, bradycardia, bundle branch block). Very rarely atrioventricular block. Arrhythmia; severe cardiac failure may occur suddenly, without premonitory ECG changes (frequency not known). *Vascular:* Very commonly thrombophlebitis. Commonly phlebitis, haemorrhage. Uncommonly thromboembolism, phlebosclerosis. Very rarely shock. Hot flushes (frequency not known). *Respiratory, thoracic and mediastinal:* Rarely respiratory disorders, swelling of the nasal mucosa, tachypnoea and dyspnoea, radiation pneumonitis Bronchospasm (frequency not known). *Gastrointestinal:* Very commonly nausea; /vomiting, mucositis, stomatitis, diarrhoea. Commonly oesophagitis, abdominal pain or burning sensation. Uncommonly gastrointestinal haemorrhage, colitis, erosive gastritis, necrotising colitis with sometimes serious infections when doxorubicin and cytarabine are combined, ulceration and necrosis of the colon. Very rarely erosions, mucosal discoloration. *Hepatobiliary:* Hepatotoxicity (frequency not known). *Skin and subcutaneous tissue:* Very commonly local toxicity, onycholysis, erythema, photosensitivity, palmar–plantar erythrodysaesthesia syndrome, alopecia, rash. Commonly pruritus, recall of skin reaction due to prior radiotherapy, skin hyperpigmentation, hyperpigmentation of nail beds, urticaria. Rarely tissue necrosis, local erythematous reactions along the vein which was used for the injection. *Musculoskeletal, connective tissue:* Very rarely generalised muscle weakness. Joint pain (frequency not known). *Renal, urinary:* Commonly haemorrhagic cystitis; local reactions (chemical cystitis) might occur at intravesical treatment (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall and bladder spasms). Red colouration of the urine 1-2 days after administration, acute renal failure, renal damage (frequency not known). *Reproductive system, breast:* Very rarely Amenorrhoea, oligospermia, azoospermia. Infertility (frequency not known). *General, administration site:* Very commonly fever, asthenia, shivering. Rarely dizziness. Very rarely general malaise. A stinging or burning sensation at the administration site (frequency not known). *Investigations:* Very commonly asymptomatic decrease in LVEF, abnormal ECG, abnormal transaminase levels, weight gain. *Surgical, medical procedure:* Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts). **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; D-22880 Wedel. **Date of revision of text**: 03/2023

Doxorubicin medac / Doxorubicin hydrochloride has been authorised in Czech Republic, Finland, Germany, Iceland, Portugal, Slovak Republic, Ukraine and United Kingdom.

Epimedac® / Epirubicin hydrochloride 2 mg/ml solution for injection

Qualitative and quantitative composition: One 5 ml / 10 ml / 25 ml / 50 ml / 100 ml vial contains 10 mg / 20 mg / 50 mg / 100 mg / 200 mg epirubicin hydrochloride. *Excipients:* Sodium chloride, hydrochloric acid, water for injections. **Therapeutic indications:** Carcinoma of the breast, advanced ovarian cancer**,** gastric cancer**, s**mall cell lung cancer. *Intravesical use:* Papillary transitional cell carcinoma of the bladder, **c**arcinoma-in-situ of the bladder, intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection. **Posology and method of administration:** For intravenous or intravesical use only. Safety and efficacy in children has not been established. *Intravenous administration:* It is advisable to administer epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Avoid extravasation! In that case administration should be stopped immediately. *Dosage:* To avoid cardiac toxicity, a total cumulative dose of 900-1,000 mg/m² epirubicin should not be exceeded. *Conventional dose:* As a single agent, the recommended dosage in adults is 60-90 mg/ m² body surface area, injected intravenously over 3-5 minutes, repeated at 21- day intervals, depending upon the patient's haematological status and bone marrow function. *Impaired liver function:* The dose should be reduced based on serum bilirubin levels (refer to SPC). *Impaired renal function:* Dosage adjustment may be necessary in patients with serum creatinine >5 mg/dl. *Intravesical use:* Instillations of 50mg/50ml (diluted with saline or water for injection), up to 80mg/50ml (depending on individual tolerability) for carcinoma-in-situ. **Contraindications:** Hypersensitivity to active substance, any excipient, other anthracyclines or anthracenediones; lactation. *Intravenous use:* Persistent myelosuppression; severe hepatic impairment; severe myocardial insufficiency; recent myocardial infarction; severe arrhythmias; previous treatment with maximal cumulative doses of epirubicin and/or other anthracyclines or anthracenediones; acute systemic infection; unstable angina pectoris; myocardiopathy; acute inflammatory heart disease, severe inflammation of the mucous membranes in the mouth and/or gastrointestinal tract. *Intravesical use:* Urinary tract infections; invasive tumours penetrating the bladder; catheterisation problems; inflammation of the bladder; hematuria; contracted bladder; large volume of residual urine. **Undesirable effects:** *Infections, infestations:* Very commonly infection, conjunctivitis. Commonly bacterial cystitis following intravesical administration. Uncommonly sepsis, pneumonia. Septic shock, cellulitis (frequency not known). *Neoplasms:* Uncommonly acute lymphocytic leukaemia, secondary acute myelogenous leukaemia with or without a pre-leukemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have short (1-3 years) latency. *Blood, lymphatic system:* Very commonly myelosuppression (leukopenia, granulocytopenia, neutropenia, anaemia, febrile neutropenia, thrombocytopenia). *Immune system:* Rarely anaphylactic reaction including skin rash, pruritus, fever and chills, allergic reactions following intravesical administration, hypersensitivity. Anaphylactic shock (frequency not known). *Metabolism, nutrition:* Commonly loss of appetite, dehydration. Rarely hyperuricemia. *Nervous system:* Rarely dizziness. Headache (frequency not known). *Eye:* Very commonly keratitis. *Cardiac:* Commonly ventricular tachycardia, AV block, bundle-branch block bradycardia, congestive heart failure (dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, extrasystoles). Rarely cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy). *Vascular:* Very commonly hot flashes, phlebitis. Commonly haemorrhage, flushing. Uncommonly embolism (arterial), hrombophlebitis. Shock, phlebosclerosis, thromboembolism (frequency not known). *Respiratory:* Uncommonly pulmonary embolism. Hypoxia as a result of myelosuppression (frequency not known). *Gastrointestinal:* Very commonly mucositis, stomatitis, vomiting, diarrhoea, nausea, which can result in loss of appetite and abdominal pain. Commonly oesophagitis, gastrointestinal pain, abdominal pain; gastrointestinal erosion, haemorrhage, ulce; oral mucosa erosion, oral pain, mucosal burning sensation. Pigmentation buccal (frequency not known). *Skin, subcutaneous tissue:* Very commonly alopecia, normally reversible, appears in 60 - 90% of treated cases; it is accompanied by lack of beard growth in males; skin toxicity. Commonly rash, pruritus, nail hyperpigmentation, skin disorders, skin hyperpigmentation, local tissue toxicity. Rarely urticaria, erythema. Photosensitivity (frequency not known). *Renal, urinary:* Very commonly chromaturia (red coloration of urine for 1 to 2 days after administration). Commonly dysuria, haematuria, pollakisuria following intravesical administration. *Reproductive system:* Commonly amenorrhea. Rarely azoospermia. *General, administration site:* Very commonly malaise, pyrexia. Commonly chills, infusion site erythema. Uncommonly asthenia. Local pain, paravenous injection can cause soft tissue necrosis (frequency not known). *Investigations:* Very commonly changes in transaminase levels. Commonly asymptomatic decreases in left ventricular ejection fraction. *Injury, poisoning and procedural:* Very commonly chemical cystitis, sometimes haemorrhagic, following intravesical administration. Hypersensitivity to irritated skin, radiation recall reaction (frequency not known). As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 03/2023

Epimedac®/ Epirubicin hydrochloride has been authorised in Denmark, Finland, France, Germany, Norway, Slovak Republic, Ukraine and United Kingdom.

Etoposide 20 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: 1 ml concentrate for solution for infusion contains 20 mg etoposide. 1 vial of 5 ml (25 ml) concentrate for solution for infusion contains 100 mg (500 mg) etoposide. *Excipients:* Citric acid (anhydrous), Polysorbate 80, Macrogol 300, Ethanol (262 mg/ml). **Therapeutic indications:** Etomedac is indicated in combination with other approved chemotherapeutic agents for the treatment of first line, recurrent or refractory testicular cancer in adults, small cell lung cancer in adults, Hodgkin's lymphoma in adult and paediatric patients, non-Hodgkin's lymphoma in adult and paediatric patients, acute myeloid leukaemia in adult and paediatric patients, first line and second line therapy for the treatment of high risk gestational trophoblastic neoplasia in adults, non-epithelial ovarian cancer in adults. Etomedac is indicated for the treatment of platinum-resistant/refractory epithelial ovarian cancer in adults. **Posology and method of administration:** The recommended dose of etoposide in adult patients is 50 to 100 mg/m^2/day on days 1 to 5 or 100 to 120 mg/m^2 on days 1, 3, and 5 every 3 to 4 weeks in combination with other drugs indicated in the disease to be treated. Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior radiotherapy or chemotherapy. Etomedac is administered by slow intravenous infusion (usually over a 30 to 60 minute period). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients; lactation. **Undesirable effects:** *Infections:* Commonly infection including opportunistic infections like pneumocystis jirovecii pneumonia. *Neoplasms:* Commonly acute leukaemia. *Blood, lymphatic system:* Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Very commonly anaemia, leukopenia, myelosuppression (fatal outcome has been reported), neutropenia, thrombocytopenia. *Immune system:* Commonly anaphylactic-type reactions that can be fatal; angioedema, bronchospasm. *Metabolism:* Tumour lysis syndrome. *Nervous system:* Commonly dizziness. Uncommonly neuropathy peripheral. Rarely cortical blindness transient, neurotoxicities (e.g. somnolence, fatigue), optic neuritis, seizure (occasionally associated with allergic reactions). *Cardiac:* Commonly arrhythmia, myocardial infarction. *Vascular:* Commonly hypertension, transient systolic hypotension following rapid intravenous administration. Uncommonly haemorrhage. *Respiratory, thoracic, mediastinal:* Rarely interstitial pneumonitis, pulmonary fibrosis; bronchospasm. *Gastrointestinal:* Very commonly abdominal pain, anorexia, constipation, nausea and vomiting. Commonly diarrhoea, mucositis (including stomatitis and oesophagitis). Rarely dysgeusia, dysphagia. *Hepatobiliary:* Very commonly alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, hepatotoxicity. *Skin, subcutaneous tissue:* Very commonly alopecia, pigmentation. Commonly pruritus, rash, urticaria. Rarely radiation recall dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, oedema of face and tongue. *Reproductive system:* Infertility. *General, administration site:* Very commonly asthenia, malaise. Commonly extravasation (local soft tissue toxicity, swelling, pain, cellulitis, necrosis including skin necrosis), phlebitis. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text** 01/2024

Etoposide 20 mg/ml has been authorised in Germany, The Netherlands and United Kingdom.

Fluorouracil Injection 25 mg/ml, solution for injection
1 vial contains 2500mg fluorouracil in 100ml solution (25mg/ml).
Fluorouracil Injection, 50 mg/ml, solution for injection
1 vial contains 500mg (1000mg; 2500mg; 5000mg) fluorouracil in 10ml (20ml; 50ml; 100ml) solution (50mg/ml).
Excipients: Sodium hydroxide, water for injections. **Therapeutic indications:** Alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon and breast, either as single agent or in combination with other cytotoxic agents. **Posology and method of administration:** Given by intravenous injection or intravenous or intra-arterial infusion. *Single agent infusion:* 15 mg/kg bodyweight but not more than 1 g per infusion, diluted in 500 ml of 5 % glucose or 0.9 % NaCl injection by intravenous infusion over 4 hours. Alternatively the daily dose may be infused over 30–60 minutes or as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity or a total dose of 12–15 g has been reached. *Single agent injection:* 12 mg/kg bodyweight daily for 3 days and then, if there is no evidence of toxicity, 6 mg/kg on alternate days for 3 further doses. An alternative regime is 15 mg/kg as a single intravenous injection once a week throughout the course. *Intra-arterial Infusion:* 5 – 7.5 mg/kg bodyweight daily by 24 hour continuous intra-arterial infusion. The initial course of fluorouracil can be repeated after an interval of 4 to 6 weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5–15 mg/kg bodyweight at weekly intervals. No recommendations for children. **Contraindications:** Hypersensitivity to fluorouracil or to any of the excipients, bone marrow depression after radiotherapy or treatment with other antineoplastic agents, management of non-malignant disease, serious liver impairment, serious infections (e.g. Herpes zoster, chickenpox), seriously debilitated patients, breast feeding women, known complete dihydropyrimidine dehydrogenase (DPD) deficiency, recent or concomitant treatment with brivudine. **Undesirable effects:** *Infections, infestations:* Very commonly infections. Uncommonly sepsis. *Blood, lymphatic system:* Very commonly Myelosuppression (Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days), neutropenia, leukopenia, granulocytopenia, thrombocytopenia, agranulocytosis, anemia, pancytopenia. Commonly febrile neutropenia. *Immune system:* Very commonly immunosuppression. Rarely generalized allergic reactions, anaphylactic reaction, anaphylactic shock. *Endocrine:* Rarely increase of T4 (total thyroxin), increase of T3 (total trijodthyronin). *Metabolism, nutrition:* Very commonly hyperuricemia. Uncommonly dehydration. Frequency unknown lactic acidosis, tumour lysis syndrome. *Psychiatric:* Uncommonly euphoria. Rarely confusion. Very rarely disorientation. *Nervous system:* Uncommonly nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramid signs, somnolence, opticus neuritis. Rarely extrapyramidalmotoric disturbances, cerebellar disturbances, cortical disturbances, peripheral neuropathy. Very rarely leuko-encephalopathy including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma. Frequency unknown hyperammonaemic encephalopathy, posterior reversible encephalopathy syndrome (PRES). *Eye:* Commonly conjunctivitis. Uncommonly excessive lacrimation, blurred vision, eye movement disturbance, diplopia, decrease in visual acuity, photophobia, blepharitis, ectropion, dacryostenosis. *Cardiac:* Very commonly ischaemic ECG abnormalities. Commonly angina pectoris-like chest pain, tachycardia. Uncommonly arrhythmia, myocarditis, myocardial ischaemia, cardiac failure, myocardial infarction, dilatative cardiomyopathy, cardiac shock. Very rarely cardiac arrest, sudden cardiac death. Frequency unknown pericarditis, stress cardiomyopathy (takotsubo syndrome). *Vascular:* Uncommonly hypotension. Rarely vasculitis, cerebral ischaemia, intestinal ischaemia, peripheral ischaemia, Raynaud's phenomenon, thromboembolism, thrombophlebitis/vein tracking. *Respiratory, thoracic, mediastinal:* Very commonly bronchospasm, epistaxis. Uncommonly dyspnea. *Gastrointestinal:* Gastrointestinal adverse events are very common and may be life-threatening: Mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), anorexia, watery diarrhoea, nausea, vomiting. Uncommonly gastrointestinal ulceration, gastrointestinal haemorrhage. Frequency unknown pneumatosis intestinalis. *Hepatobiliary:* Uncommonly liver cell damage. Very rarely liver necrosis (cases with fatal outcome), biliary sclerosis, cholecystitis. *Skin, subcutaneous tissue:* Very commonly alopecia, palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) has been noted with protracted and high dose continuous infusion. The syndrome begins with dysaesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. Uncommonly dermatitis, skin alterations (e.g. dry skin, fissure erosion, erythema, pruritic maculopapular rash), exanthema, urticaria, photosensitivity, hyperpigmentation, hypopigmentation, streaky hyperpigmentation or depigmentation near the veins, nail disorders (e.g. diffuse superficial blue pigmentation, nail hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia), onycholysis, recall phenomenon. Frequency unknown cutaneous lupus erythematosus. *Renal, urinary:* Very rarely renal failure. *Reproductive system:* Uncommonly spermatogenesis and ovulation disorder. *General, administration site:* Very commonly fever, delayed wound healing, fatigue, malaise, weakness. See SmPC for details of other adverse events.
Basic NHS price:
5-FU 25mg/ml: 2500 mg/100ml £ 32.00
5-FU 50 mg/ml: 500 mg /10 ml £ 6.40 1000 mg/20 ml £ 12.80
2500 mg/50ml £ 32.00 5000 mg/100ml £ 64.00
Legal classification: POM.
Marketing authorisation holder: medac GmbH, Theaterstraße 6; 22880 Wedel, Germany.
Product information in the UK: medac Pharma, Scion House, Stirling University Innovation Park, Stirling FK9 4NF. T:01786 458086, F:01786 458032. info@medacpharma.co.uk
Marketing authorisation numbers: PL 11587/0021 (5-FU 25mg/ml), PL 11587/0015 (5-FU 50mg/ml).
Date of revision of text: 11/2021

Levofolic® / Levofolinic acid 50 mg/ml solution for injection or infusion

Qualitative and quantitative composition: Each ml of solution contains 54.65 mg disodium levofolinate equivalent to 50 mg levofolinic acid. Each 1 ml (4 ml; 9 ml) vial contains 54.65 (218.6; 491.85) mg disodium levofolinate equivalent to 50 mg (200 mg; 450 mg) levofolinic acid. *Excipients:* Sodium hydroxide, hydrochloric acid, water for injections. **Therapeutic indications:** To diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children; in combination with 5-FU in cytotoxic therapy. **Posology and method of administration:** Levofolinic acid 50 mg/ml is administered intravenously, either undiluted by injection or by infusion after dilution. It should not be administered intrathecally. Disodium levofolinate in combination with 5-FU in cytotoxic therapy: The combined use of disodium levofolinate and fluorouracil is reserved for physicians experienced in the combination of folinates with 5-FU in cytotoxic therapy. *Bimonthly regimen:* 100 mg/m² levofolinic acid by intravenous infusion over two hours, followed by bolus 400 mg/m² of 5-FU and 22-hour infusion of 5-FU (600 mg/m²) for 2 consecutive days, every 2 weeks on days I and 2. *Weekly regimen:* 10 mg/m² levofolinic acid by bolus i.v. injection or 100 to 250 mg/m² levofolinic acid as i.v. infusion over a period of 2 hours plus 500 mg/m² 5-FU as i.v. bolus injection in the middle or at the end of the disodium levofolinate infusion. *Monthly regimen:* 10 mg/m² levofolinic acid by bolus i.v. injection or 100 to 250 mg/m² levofolinic acid as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-FU as i.v. bolus injection during 5 consecutive days. For the combination therapy with 5-FU, modification of the 5-FU dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-FU. A reduction of disodium levofolinate dosage is not required. There are no data on the use of these combinations in children. **Contraindications:** Known hypersensitivity to the active substance or to any of the excipients. Disodium levofolinate is not suitable for the treatment of pernicious anaemia or other anaemias due to vitamin B12 deficiency. Although haematological remissions may occur, the neurological manifestations remain progressive. Combination of disodium levofolinate with fluorouracil: Existing contraindications against fluorouracil or severe diarrhoea. Patients who have symptoms of gastrointestinal toxicity of any severity until those symptoms have completely resolved. Patients with diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur. Pregnancy: During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the medicinal product to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy, there are no limitations as to the use of disodium levofolinate to diminish toxicity or counteract the effects. 5-FU use is generally contraindicated during pregnancy and breast-feeding; this applies also to the combined use of disodium levofolinate with 5-FU. Lactation: Disodium levofolinate alone can be used during breast feeding when considered necessary according to the therapeutic indications. However, MTX or 5-FU must not be given to breast-feeding woman. **Undesirable effects:** *All therapeutic indications: Immune system:* Very rarely allergic reactions including anaphylactoid reactions and urticaria. *Psychiatric:* Rarely insomnia, agitation and depression after high doses. *Nervous system:* Rarely increase in the frequency of attacks in epileptics. *Gastrointestinal:* Rarely gastrointestinal disorders after high doses. *General, administration site conditions:* Uncommonly fever has been observed after administration of disodium levofolinate as solution for injection. *Combination therapy with 5-FU:* Generally, the safety profile depends on the applied regimen of 5-FU due to enhancement of the 5-FU induced toxicities. *Blood, lymphatic system:* Bone marrow failure, including fatal cases. *Metabolism, nutrition:* Hyperammonaemia. *Skin, subcutaneous tissue:* Palmar-plantar erythrodysaesthesia. *General, administration site conditions:* Mucositis, including stomatitis and cheilitis. Fatalities have occurred as a result of mucositis. *Gastrointestinal:* Vomiting and nausea; diarrhoea with higher grades of toxicity and dehydration resulting in hospital admission for treatment and even death. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstr. 6, 22880 Wedel, Germany. **Date of revision of text**: 03/2020

Levofolic® / Levofolinic acid 50 mg/ml has been authorised in Belgium, Estonia, Finland, France, Italy, Latvia, Lithuania, Poland, Portugal, Slovak Republic, Slovenia, Sweden and United Kingdom.

Sodiofolin 50 mg/ml, solution for injection/infusion

Qualitative and quantitative composition: Sodiofolin contains 54.65 mg/ml disodium folinate equivalent to 50 mg/ml folinic acid. 2 ml (4ml; 6ml; 8ml; 10ml; 18ml) of solution contain 109.3mg (218.6mg; 327.9mg; 437.2mg; 546.5mg; 983.7mg) disodium folinate equivalent to 100 (200; 300; 400; 500; 900) mg folinic acid. *Excipients:* Sodium hydroxide, hydrochloric acid, water for injection. **Therapeutic indications:** Disodium folinate is indicated**:** - to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, the procedure is commonly known as "Folinate Rescue"; - in combination with 5-fluorouracil in cytotoxic therapy. *Note:* Persistently high serum methotrexate levels may also be expected in low-dose methotrexate therapy particularly in pleural effusions, ascites, renal insufficiency and inadequate fluid intake during methotrexate therapy. **Posology and method of administration:** Sodiofolin is administered intravenously, either undiluted by injection or by infusion after dilution. The combined use of disodium folinate and fluorouracil is reserved for physicians experienced in the combination of folinates with 5-fluorouracil in cytotoxic therapy. Different regimes and different dosages are used, without any dosage having been proven to be the optimal one. **Contraindications:** Known hypersensitivity to disodium folinate or any of the excipients. The combination of disodium folinate with fluorouracil is not indicated in: existing contraindications against fluorouracil, in particular pregnancy and lactation, severe diarrhoea. Therapy with disodium folinate combined with fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity until those symptoms have completely resolved. Patients with diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur. Regarding the use of folinic acid with methotrexate or 5 fluorouracil during pregnancy and lactation, see summaries of product characteristics for methotrexate- and 5 fluorouracil-containing medicinal products. Disodium folinate is not suitable for the treatment of pernicious anaemia or other anaemias due to Vitamin B12 deficiency. Although haematological remissions may occur, the neurological manifestations remain progressive. **Undesirable effects:** *All therapeutic indications: Immune system:* Very rarely allergic reactions - sensitisation, including anaphylactoid reactions and urticaria. *Psychiatric:* Rarely insomnia, agitation and depression after high doses. *Nervous system:* Rarely increase in the frequency of attacks in epileptics. *Gastrointestinal:* Rarely gastrointestinal disorders after high doses. *General, administration site:* Uncommonly fever after administration as solution for injection. *Combination therapy with 5 fluorouracil:* Disodium folinate enhances the toxicity of 5 fluorouracil. Generally, the safety profile depends on the applied regimen of 5 fluorouracil. *Blood, lymphatic system:* Bone marrow failure, including fatal cases. *Metabolism, nutrition:* Hyperammonaemia. *Skin, subcutaneous tissue:* Palmar-plantar erythrodysaesthesia. *General, administration site:* Mucositis, including stomatitis and cheilitis. Fatalities as result of mucositis. *Gastrointestinal:* Vomiting, nausea; diarrhoea with higher grades of toxicity, dehydration resulting in hospital admission for treatment and even death. **Legal classification:** POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text:** 11/2020

Sodiofolin 50 mg/ml has been authorized in Germany, Kazakhstan, Russia and United Kingdom (not all strengths are authorized in all countries).

Irinotecan (Hydrochloride) medac 20 mg/mL, concentrate for solution for infusion
Qualitative and quantitative composition: 1 mL of the concentrate for solution for infusion contains 20 mg irinotecan hydrochloride trihydrate, equivalent to 17.33 mg irinotecan. Each vial of 2 mL (5 mL; 15 mL; 25 mL; 50 mL) contains 40 mg (100 mg; 300 mg; 500 mg; 1000 mg) of irinotecan hydrochloride trihydrate. *Excipients:* Sorbitol 45mg/mL, lactic acid, sodium hydroxide, water for injections. **Therapeutic indications:** Treatment of patients with advanced colorectal cancer: In combination with 5-FU and folinic acid in patients without prior chemotherapy for advanced disease; as single agent in patients who have failed an established 5-FU containing treatment regimen. In combination with cetuximab for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer without prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy. In combination with 5-FU, folinic acid and bevacizumab for first-line treatment of patients with metastatic carcinoma of the colon or rectum. In combination with capecitabine with or without bevacizumab for first-line treatment of patients with metastatic colorectal carcinoma. **Posology and method of administration:** For adults only. After dilution the irinotecan solution for infusion should be infused into a peripheral or central vein. *Recommended dosage:* In monotherapy for previously treated patients 350 mg/m² as an intravenous infusion over a 30- to 90-minute period every 3 weeks. Irinotecan plus 5-FU/FA: In every-2-weeks schedule 180 mg/m² of irinotecan once every 2 weeks as an intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and 5-FU. In the weekly schedule, the administration of irinotecan at 80 mg/m² is followed by infusion with folinic acid and then by 5-FU over 6 weeks. For other combinations and dosage adaptions refer to SPC. *Impaired renal function:* not recommended. *Elderly:* Dose should be chosen carefully. **Contraindications:** Chronic inflammatory bowel disease and/or bowel obstruction; hypersensitivity to active substance or to any of the excipients; breast-feeding; bilirubin > 3 times the ULN; severe bone marrow failure; WHO performance status > 2; concomitant use with St.John's wort; live attenuated vaccines. For additional contraindications of cetuximab, bevacizumab or capecitabine, refer to the product information for these products. **Undesirable effects:** *Infections, infestations:* Commonly infection. Frequency not known: Pseudomembranous colitis one of which has been documented bacteriologically (Clostridium difficile), sepsis, fungal infections (e.g. pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, systemic candida), viral infections (e.g. herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis). *Blood and lymphatic system:* Very commonly neutropenia, anaemia, thrombocytopenia. Commonly febrile neutropenia. Frequency not known: Thrombocytopenia with antiplatelet antibodies. *Immune system:* Frequency not known: Hypersensitivity, anaphylactic reaction. *Metabolism, nutrition:* Very commonly decreased appetite. Frequency not known: Dehydration (due to diarrhoea and vomiting), hypovolaemia. *Nervous system:* Very commonly cholinergic syndrome. Frequency not known: Speech disorder generally transient in nature (in some cases, attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan), paraesthesia, muscular contractions involuntary. *Cardiac:* Frequency not known: Hypertension (during or after infusion), cardio circulatory failure (in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis). *Vascular:* Frequency not known: Hypotension (in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis). *Respiratory, thoracic and mediastinal:* Uncommonly interstitial lung disease presenting as lung infiltration, early effects such as dyspnoea. Frequency not known: Dyspnoea, hiccups. *Gastrointestinal:* Very commonly diarrhoea, vomiting, nausea, abdominal pain. Commonly constipation. Frequency not known: Intestinal obstruction, ileus (cases of ileus without preceding colitis have also been reported), megacolon, gastrointestinal haemorrhage, colitis (in some cases complicated by ulceration, bleeding, ileus, or infection), typhlitis, colitis ischaemic, colitis ulcerative, symptomatic or asymptomatic pancreatic enzymes increase, intestinal perforation. *Hepatobiliary:* Frequency not known: Steatohepatitis, hepatic steatosis. *Skin, subcutaneous tissue:* Very commonly reversible alopecia. Frequency not known: Skin reaction. *Musculoskeletal, connective tissue:* Frequency not known: Cramps. *Renal, urinary:* Frequency not known: Renal impairment, acute renal failure generally in patients who become infected and/or volume depleted from severe gastrointestinal toxicities, renal insufficiency (in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis). *General, administration site:* Very commonly mucosal inflammation, pyrexia, asthenia. Frequency not known: Infusion site reaction. *Investigations:* Very commonly transaminases (ALT and AST) increased, blood bilirubin increased, blood alkaline phosphatase increased. Commonly blood creatinine increased. Very rarely transaminases increased (i.e. AST and ALT) in the absence of progressive liver metastasis. Frequency not known: Amylase increased, lipase increased, hypokalaemia, hyponatraemia mostly related with diarrhoea and vomiting. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 10/2022
Irinotecan medac has been authorised in Finland, France, Germany, Pakistan and United Kingdom.

Methotrexate 100 mg/ml solution for injection

Qualitative and quantitative composition: One vial with 10 ml (50 ml) contains 1,000 mg (5,000 mg) methotrexate. *Excipients:* Sodium hydroxide, water for injections. **Therapeutic indications:** Acute lymphocytic leukemia in combination with other cytotoxics; Non-Hodgkin's lymphomas in combination with other cytotoxics in adult patients with NHL of intermediate and high degree of malignancy or in pediatric patients; head and neck cancer as palliative monotherapy in patients with metastatic or recurrent disease; breast cancer in combination with other cytotoxics for adjuvant treatment after tumor resection or mastectomy and for palliative treatment in advanced disease; choriocarcinoma and similar trophoblastic diseases as monotherapy in patients with good prognosis (low risk) or in combination with other cytotoxics in patients with poor prognosis (high risk); osteosarcoma in combination with other cytotoxics for adjuvant and neoadjuvant therapy; cancer of the bladder in combination with other cytotoxics. **Posology and method of administration:** Treatment regimen should be decided on an individual patient basis, with reference to current treatment protocols. MTX can be applied in the form of an intravenous, intramuscular, or intra-arterial injection as well as an intravenous infusion. Within the scope of therapy with high doses, MTX is administered as a continuous intravenous infusion (glucose, isotonic saline). Doses are usually based on the patient's body weight or body surface area (BSA). Total doses greater than 100 mg are usually given by intravenous infusion. MTX 100 mg/ml solution for injection is a hypertonic presentation and therefore not suitable for intrathecal and intraventricular use. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; liver insufficiency; pronounced functional impairment of the haematopoietic system such as anaemia, leucopenia, and/or thrombocytopenia (e.g. following prior radio- or chemotherapy); bone marrow suppression ; severe active infections; overt or laboratory evidence of immunodeficiency syndrome(s), breast-feeding; renal insufficiency (creatinine clearance < 60 ml/min); alcohol abuse; stomatitis, gastrointestinal ulceration. **Undesirable effects:** Occurrence and severity of undesirable effects depend on dose level and frequency of methotrexate administration. *Infections, infestations:* Commonly herpes zoster. Uncommonly opportunistic infections (sometimes fatal), including pneumonia. Rarely sepsis. Very rarely nocardiosis, histoplasmosis, cryptococcosis, herpes simplex hepatitis, disseminated herpes simplex, cytomegalovirus infection, cytomegalovirus pneumonia, septicaemia. *Neoplasm:* Uncommonly malignant lymphomas. Very rarely tumour lysis syndrome. *Blood, lymphatic system:* Very commonly leukopenia, thrombocytopenia. Commonly anaemia up to pancytopenia, myelosuppression, agranulocytosis. Rarely megaloblastic anaemia. Very rarely aplastic anaemia, eosinophilia, neutropenia, lymphadenopathy, lymphoproliferative disorders. Frequency not known: haemorrhages, haematoma. *Immune system:* Very commonly allergic reactions, anaphylactic shock, allergic vasculitis, immunosuppression, fever. Very rarely hypogammaglobulinaemia. *Metabolism, nutrition:* Uncommonly diabetes. Frequency not known: malabsorption, metabolic disorder. *Psychiatric:* Uncommonly depression. Rarely mood alteration, transient perceptual disturbances. Frequency not known: psychosis. *Nervous system:* Commonly headaches, dizziness, drowsiness. Uncommonly convulsions, hemiparesis, leukoencephalopathy/ encephalopathy, vertigo, cognitive dysfunction. Rarely paresis, dysarthria, aphasia, myelopathy. Very rarely unusual cranial sensations, myasthenia, paraesthesia, acute aseptic meningitis. *Eye:* Rarely impairment of vision, serious visual changes of not known aetiology, blurred vision. Very rarely transient blindness/vision loss, periorbital oedema, blepharitis, conjunctivitis, epiphora, photophobia. *Cardiac:* Rarely hypotension. Very rarely pericarditis, pericardial effusion, pericardial tamponade, sudden death. *Vascular:* Uncommonly vasculitis. Rarely thromboembolic complications (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis). *Respiratory, thoracic, mediastinal:* Commonly interstitial pneumonitis, alveolitis sometimes fatal. Uncommonly pulmonary fibrosis, pleuritic pain and pleural thickening. Rarely pharyngitis. Very rarely chronic interstitial obstructive pulmonary disease, asthma-like symptoms (e.g. cough, dyspnoea, impaired pulmonary function test), pneumocystis carinii pneumonia. Frequency not known: acute pulmonary oedema. *Gastrointestinal:* Very commonly stomatitis, abdominal pain, anorexia, nausea, vomiting. Commonly diarrhoea. Uncommonly ulcerative stomatitis, haemorrhagic gastroenteritis, pancreatitis. Rarely enteritis, gingivitis, melena. Very rarely hematemesis. Frequency not known: toxic megacolon. When stomatitis or diarrhoea occur, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or perforation or dehydration. *Liver:* Commonly elevated transaminases, bilirubin and alkaline phosphatase. Uncommonly chronic cirrhosis and fibrosis, decrease in serum albumins, fatty liver. Rarely hepatotoxicity, acute hepatitis. Very rarely acute liver necrosis, liver failure, reactivation of chronic hepatitis. Frequency not known: reactivation of hepatitis B, worsening of hepatitis C. *Skin, subcutaneous tissue:* Commonly erythema, pruritus, exanthema. Uncommonly alopecia, Stevens-Johnson syndrome, extensive herpetiform skin eruptions, toxic epidermic necrolysis (Lyell syndrome), urticaria, photosensitivity, pigmentary changes, impaired wound healing. Rarely acne, ecchymoses, erythema multiforme, nodulosis, hyperpigmentation of the nails, onycholysis, increase in rheumatic nodules. Very rarely acute paronychia, furunculosis, telangiectasia. Frequency not known: Skin exfoliation / dermatitis exfoliative, skin necrosis, petechiae. With concomitant UV therapy psoriatic lesions can worsen. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate. *Musculoskeletal, connective tissue:* Uncommonly arthralgia, myalgia, osteoporosis. Rarely stress fractures. Frequency not known: aseptic necrosis of the femoral head, osteonecrosis of jaw (secondary to lymphoproliferative disorders). *Renal, urinary:* Very commonly decreased creatinine clearance. Uncommonly severe nephropathy, renal failure, cystitis, dysuria, oliguria, anuria. Rarely hyperuricemia, elevated serum creatinine and urea level. Very rarely azotaemia, haematuria, proteinuria. *Pregnancy:* Uncommonly foetal defects. Rarely abortion. Very rarely foetal death. *Reproductive system:* Uncommonly vaginal inflammation and ulceration. Rarely menstrual dysfunction. Very rarely defective oogenesis or spermatogenesis, loss of libido/impotence, transient oligospermia, vaginal discharge, gynaecomastia. Intravenous administration of MTX may also result in acute encephalitis and acute encephalopathy with fatal outcome. *Adverse reactions following intramuscular administration:* After intramuscular administration, local reactions (burning sensation) or injuries (sterile abscesses, loss of adipose tissue) at the injection site may occur. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 01/2023

Methotrexate 100 mg/ml solution for injection has been authorised in Germany, Kazakhstan and United Kingdom.

Mitomycin medac 1 mg/ml powder for solution for injection/infusion or intravesical use

Qualitative and quantitative composition: Each vial of Mitomycin medac contains 2 mg (10 mg / 20 mg / 40 mg) mitomycin. *Excipient:* Urea. **Therapeutic indications:** Mitomycin is used in palliative tumour therapy. Intravenous use of mitomycin is indicated as monochemotherapy or in combined cytostatic chemotherapy in adults with advanced colorectal, gastric, oesophageal, cervical, pancreatic carcinoma, advanced and/or metastatic breast carcinoma; non-small-cell bronchial carcinoma; advanced tumours of the head and neck. Mitomycin medac is indicated as intravesical administration for relapse prevention in adults with superficial urinary bladder carcinoma after transurethral resection. **Posology and method of administration:** *Intravenous administration:* It is essential that the injection is administered intravenously. If the medicinal product is injected perivasally, extensive necrosis occurs in the area concerned. In cytostatic monochemotherapy, mitomycin is usually administered intravenously as a bolus injection. The recommended doses are 10-20 mg/m^2 body surface area every 6-8 weeks, 8-12 mg/m^2 body surface area every 3-4 weeks or 5-10 mg/m^2 of body surface every 3-6 weeks, depending on the therapeutic scheme used. In combination therapy, the dose is considerably lower. *For intravesical use following reconstitution:* Unless otherwise specified, the dose of mitomycin is 40 mg mitomycin instilled into the bladder once weekly. Regimens with instillations every 2 weeks, every month or 3 monthly can also be used. The specialist should decide on the optimum regime, frequency and duration of therapy on an individual patient basis. The urine pH should be higher than pH 6. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, breastfeeding. *Systemic therapy:* Pancytopenia, isolated leukopenia or thrombocytopenia, haemorrhagic diathesis and acute infections are absolute contraindications. Restrictive or obstructive disturbances to pulmonary ventilation, renal dysfunction, hepatic dysfunction and/or a poor general state of health are relative contraindications. Temporal connection with radiotherapy or other cytostatics may be a further contraindication. *Intravesical therapy:* Bladder wall perforation, cystitis. **Undesirable effects:** *Systemic therapy: Blood, lymphatic system:* Very commonly bone marrow suppression, leukopenia, thrombocytopenia. Rarely haemolytic anaemia, thrombotic microangiopathy (TMA), incl. thrombotic thrombocytopenic purpura (TTP). Anaemia (frequency not known). *Infections, infestations:* Rarely life-threatening infection, sepsis. Infection (frequency not known). *Immune system:* Very rarely severe allergic reaction. *Cardiac:* Rarely heart failure after previous therapy with anthracyclines. *Respiratory, thoracic and mediastinal:* Commonly interstitial pneumonia, dyspnoea, cough, shortness of breath. Rarely pulmonary hypertension, pulmonary veno-occlusive disease (PVOD). *Gastrointestinal:* Very commonly nausea, vomiting. Uncommonly mucositis, stomatitis, diarrhoea, anorexia. *Hepatobiliary:* Rarely liver dysfunction, increased transaminases, icterus, veno-occlusive disease (VOD) of the liver. *Skin, subcutaneous tissue:* Commonly exanthema, allergic skin rash, contact dermatitis, palmar-plantar erythema. Uncommonly alopecia. Rarely generalised exanthema. *Renal, urinary:* Commonly renal dysfunction, increase in serum creatinine, glomerulopathy, nephrotoxicity. Rarely haemolytic uraemic syndrome (HUS) commonly fatal, microangiopathic-haemolytic anaemia (MAHA syndrome). *General, administration site:* Commonly cellulitis, tissue necrosis following extravasation. Uncommonly fever. *Intravesical therapy: Skin, subcutaneous tissue:* Commonly pruritus, allergic skin rash, contact dermatitis, palmar-plantar erythema. Rarely generalised exanthema. *Renal, urinary:* Commonly cystitis (possibly haemorrhagic), dysuria, nocturia, pollakisuria, haematuria, local irritation of the bladder wall. Very rarely necrotising cystitis, allergic (eosinophilic) cystitis, stenosis of the efferent urinary tract, reduction in bladder capacity, bladder wall calcification and bladder wall fibrosis, bladder perforation. In case of extravasation: bladder perforation, (fat) tissue necrosis of the surrounding area, vesical fistula, abscesses (frequency not known). After intravesical administration, only minor amounts of mitomycin reach the systemic circulation. Nevertheless, in very rare cases the following systemic adverse reactions have been reported: Leukocytopenia, thrombocytopenia; interstitial lung disease; nausea, vomiting, diarrhoea; transaminases increased; alopecia; renal dysfunction; fever. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text:** 11/2020

Mitomycin medac has been authorised in Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Italy, Lithuania, Norway and Slovak Republic (not all strengths are authorized in all countries)

Oxaliplatin medac, 5 mg/ml, powder for solution for infusion

Qualitative and quantitative composition: One vial with lyophilised powder contains 50mg/ 100mg/ 150mg oxaliplatin. One ml of reconstituted concentrate solution contains 5mg oxaliplatin. Each vial contains 50mg (100mg; 150mg) oxaliplatin in 10ml (20ml; 30ml) of solvent. Excipients: Lactose monohydrate. **Therapeutic indications:** In combination with 5-fluorouracil (5-FU) and folinic acid (FA): - adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumor; - treatment of metastatic colorectal cancer. **Posologie and method of administration:** Recommended dose for oxaliplatin: in adjuvant setting 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months); in treatment of metastatic colorectal cancer 85 mg/m² intravenously repeated every 2 weeks until disease progression or unacceptable toxicity. Dosage given should be adjusted according to tolerability. Oxaliplatin should always be administered before fluoropyrimidines. It is administered as a 2- to 6-hour intravenous infusion in 250 to 500ml of 5% glucose solution. **Contraindications:** Known history of hypersensitivity to oxaliplatin or excipients; breast feeding; myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 2 x 10^9/l and/or platelet count of < 100 x 10^9/l; peripheral sensitive neuropathy with functional impairment prior to first course; severely impaired renal function (creatinine clearance <30 ml/min). **Undesirable effects:** The most frequent adverse events of oxaliplatin in combination with 5-FU/FA were gastrointestinal (diarrhea, nausea, vomiting, mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone. ***Infections, infestations:*** *Very common:* Infection. *Common:* Rhinitis, upper respiratory tract infection, neutropenic sepsis. *Uncommon:* Sepsis. *Frequency unknown:* Septic shock. ***Blood, lymphatic system:*** *Very common:* Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia. *Common:* Febrile neutropenia. *Rare:* Immunoallergic thrombocytopenia, haemolytic anaemia, disseminated intravascular coagulation (DIC) including fatal outcomes. *Frequency unknown:* Haemolytic uremic syndrome, (autoimmune) pancytopenia, secondary leukaemia. ***Immune system:*** *Very common:* Frequent allergy/allergic reactions (such as skin rash, in particularly urticaria, conjunctivitis, rhinitis), occurring mainly during perfusion, sometimes fatal. *Common*: Anaphylactic reactions, including bronchospasm, angioedema, low blood pressure and anaphylactic shock. Delayed hypersensitivity has also been reported hours or even days after infusion. ***Metabolism, nutrition:*** *Very common:* Anorexia, hyperglycaemia, hypokalaemia, hypernatraemia. *Common:* Dehydration. *Uncommon:* Metabolic acidosis. ***Psychiatric:*** *Common:* Depression, insomnia. *Uncommon:* Nervousness. ***Nervous system:*** *Very common:* Peripheral sensory neuropathy, sensory disturbance, dysgeusia, headache. *Common:* Dizziness, motor neuritis, meningism. *Rare:* Dysarthria, reversible posterior leukoencephalopathy syndrome (RPLS). *Frequency unknown:* Convulsion, ischaemic and haemorrhagic cerebrovascular disorder. The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. Duration of symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles. The functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. Acute neurosensory manifestations start within hours of administration and often occur on exposure to cold, present as transient paraesthesia, dysaesthesia and hypoesthesia or acute syndrome of pharyngolaryngeal dysaesthesia. Other symptoms include jaw spasm, muscle spasms, muscle contractions-involuntary, muscle twitching, myoclonus, coordination abnormal, gait abnormal, ataxia, balance disorders, throat or chest tightness, pressure, discomfort, pain, cranial nerve dysfunctions, ptosis, diplopia, aphonia, dysphonia, hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation, trigeminal neuralgia/facial pain/eye pain, loss of deep tendon reflex and Lhermitte's sign. ***Eye:*** *Common:* Conjunctivitis, visual disturbance. *Rare:* Visual acuity reduced transiently; visual field disturbances; optic neuritis; transient vision loss, reversible following therapy discontinuation. ***Ear, labyrinth:*** *Uncommon:* Ototoxicity. *Rare:* Deafness. ***Cardiac:*** *Frequency unknown:* Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab. ***Vascular:*** *Common:* Haemorrhage, flushing, deep vein thrombosis, hypertension. ***Respiratory system:*** *Very common:* Dyspnoea, cough, epistaxis. *Common:* Hiccups, pulmonary embolism. *Rare:* Interstitial lung disease (sometimes fatal), pulmonary fibrosis. *Frequency unknown:* Laryngospasm, (broncho)pneumonia. ***Gastrointestinal:*** *Very common:* Nausea, diarrhoea, vomiting, stomatitis / mucositis, abdominal pain, constipation. *Common:* Dyspepsia, gastroesophageal reflux, gastrointestinal or rectal haemorrhage. *Uncommon:* Ileus, intestinal obstruction. *Rare:* Colitis including Clostridium difficile diarrhoea, pancreatitis. Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil. *Frequency unknown:* Intestinal ischemia, gastrointestinal ulcer and perforation, oesophagitis. ***Hepatobiliary:*** *Very rare:* Liver sinusoidal obstruction syndrome (veno-occlusive disease of liver) or pathological manifestations including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. *Frequency not known:* Focal nodular hyperplasia. ***Skin, subcutaneous tissue:*** *Very common:* Skin disorder, alopecia. *Common:* Skin exfoliation (i.e. hand and foot syndrome), rash erythematous, rash, hyperhidrosis, nail disorder. *Frequency unknown:* Hypersensitivity vasculitis. ***Musculoskeletal, connective tissue:*** *Very common:* Back pain. *Common:* Arthralgia, bone pain. *Frequency unknown:* Rhabdomyolysis. ***Renal and urinary:*** *Common:* Haematuria, dysuria, micturition frequency abnormal. *Very rare:* Acute tubular necrosis, acute interstitial nephritis, acute renal failure. ***General, application site:*** *Very common:* Fatigue, fever, rigors, asthenia, pain. Injection site reaction including local pain, redness, swelling and thrombosis. Extravasation may result in local pain, severe inflammation and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein. ***Investigations:*** *Very common:* Hepatic enzyme, blood alkaline phosphatise, blood bilirubin, blood lactate dehydrogenase increase; weight increase (adjuvant setting). *Common:* Blood creatinine increase; weight decrease (metastatic setting). ***Injury, poisoning:*** *Common:* Fall. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 08/2022

Oxaliplatin medac has been authorised in Germany, Indonesia, Ireland, Jordan, Pakistan and Serbia (Quatalia)

Oxaliplatin medac 5 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: 1 ml concentrate for solution for infusion contains 5 mg oxaliplatin. 10 ml (20 ml; 40 ml) of concentrate for solution for infusion contain 50 mg (100 mg; 200 mg) of Oxaliplatin. *Excipients:* Water for injections. **Therapeutic indications:** In combination with 5-fluorouracil (5-FU) and folinic acid (FA): - adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor; - treatment of metastatic colorectal cancer. **Posologie and method of administration:** Recommended dose for oxaliplatin: in adjuvant setting 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months); in treatment of metastatic colorectal cancer 85 mg/m² intravenously repeated every 2 weeks until disease progression or unacceptable toxicity. Dosage given should be adjusted according to tolerability. Oxaliplatin should always be administered before fluoropyrimidines. It is administered as a 2- to 6-hour intravenous infusion in 250 to 500ml of 5% glucose solution. **Contraindications:** Hypersensitivity to oxaliplatin or excipients; breast feeding; myelosuppression prior to starting first course, as evidenced by baseline neutrophils < 2 x 10^9/l and/or platelet count of < 100 x 10^9/l; peripheral sensitive neuropathy with functional impairment prior to first course; severely impaired renal function (creatinine clearance <30 ml/min). **Undesirable effects:** The most frequent adverse events of oxaliplatin in combination with 5-FU/FA were gastrointestinal (diarrhea, nausea, vomiting, mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone. ***Infections, infestations:*** *Very common:* Infection. *Common:* Rhinitis, upper respiratory tract infection, neutropenic sepsis. *Uncommon:* Sepsis. *Frequency unknown:* Septic shock. ***Blood, lymphatic system:*** *Very common:* Anemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia. *Common:* Febrile neutropenia. *Rare:* Immunoallergic thrombocytopenia, haemolytic anemia, disseminated intravascular coagulation (DIC). *Frequency unknown:* Haemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia. ***Immune system:*** *Very common:* Frequent allergy/allergic reactions (such as skin rash, in particularly urticaria, conjunctivitis, rhinitis), occurring mainly during perfusion, sometimes fatal. *Common*: Anaphylactic reactions, including bronchospasm, angioedema, low blood pressure and anaphylactic shock. Delayed hypersensitivity has also been reported hours or even days after infusion. ***Metabolism, nutrition:*** *Very common:* Anorexia, hyperglycaemia, hypokalaemia, hypernatraemia. *Common:* Dehydration, Hypocalcaemia. *Uncommon:* Metabolic acidosis. ***Psychiatric:*** *Common:* Depression, insomnia. *Uncommon:* Nervousness. ***Nervous system:*** *Very common:* Peripheral sensory neuropathy, sensory disturbance, dysgeusia, headache. *Common:* Dizziness, motor neuritis, meningism. *Rare:* Dysarthria, reversible posterior leukoencephalopathy syndrome (RPLS). *Frequency unknown:* Convulsion, ischemic and haemorrhagic cerebrovascular disorder. The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. Symptoms in up to 95 % of patients. Duration of symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles. The functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. Risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10%, for a cumulative dose of 1020 mg/m² (12 cycles) 20%. In the majority of the cases, the symptoms improve or totally recover when treatment is discontinued. Acute neurosensory manifestations start within hours of administration and often occur on exposure to cold, present as transient paraesthesia, dysaesthesia and hypoesthesia or acute syndrome of pharyngolaryngeal dysaesthesia. Other symptoms include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain, cranial nerve dysfunctions, ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation, trigeminal neuralgia/facial pain/eye pain, loss of deep tendon reflex and Lhermitte's sign. ***Eye:*** *Common:* Conjunctivitis, visual disturbance. *Rare:* Visual acuity reduced transiently; visual field disturbances; optic neuritis; transient vision loss, reversible following therapy discontinuation. ***Ear, labyrinth:*** *Uncommon:* Ototoxicity. *Rare:* Deafness. ***Vascular:*** *Common:* Haemorrhage, flushing, deep vein thrombosis, hypertension. ***Respiratory system:*** *Very common:* Dyspnoea, cough, epistaxis. *Common:* Hiccups, pulmonary embolism. *Rare:* Interstitial lung disease (sometimes fatal), pulmonary fibrosis. *Frequency unknown:* Laryngospasm, bronchopneumonia. ***Gastrointestinal:*** *Very common:* Nausea, diarrhoea, vomiting, stomatitis / mucositis, abdominal pain, constipation. *Common:* Dyspepsia, gastroesophageal reflux, gastrointestinal or rectal haemorrhage. *Uncommon:* Ileus, intestinal obstruction. *Rare:* Colitis including Clostridium difficile diarrhoea, pancreatitis. Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil. *Frequency unknown:* Intestinal ischemia, gastrointestinal ulcer and perforation, oesophagitis. ***Hepatobiliary:*** *Very rare:* Liver sinusoidal obstruction syndrome (veno-occlusive disease of liver) or pathological manifestations including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. *Frequency not known:* Focal nodular hyperplasia. ***Skin, subcutaneous tissue:*** *Very common:* Skin disorder, alopecia. *Common:* Skin exfoliation (i.e. hand and foot syndrome), rash erythematous, rash, hyperhidrosis, nail disorder. *Frequency unknown:* Hypersensitivity vasculitis. ***Musculoskeletal, connective tissue:*** *Very common:* Back pain. *Common:* Arthralgia, bone pain. *Frequency unknown:* Rhabdomyolysis. ***Renal and urinary:*** *Common:* Haematuria, dysuria, micturition frequency abnormal. *Very rare:* Acute tubular necrosis, acute interstitial nephritis, acute renal failure. ***Cardiac:*** *Frequency unknown:* Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab. ***General, application site:*** *Very common:* Fatigue, fever, asthenia, pain. Injection site reaction including local pain, redness, swelling and thrombosis. Extravasation may result in local pain, severe inflammation and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein. ***Investigations:*** *Very common:* Hepatic enzyme, blood alkaline phosphatase, blood bilirubin, blood lactate dehydrogenase increase; weight increase (adjuvant setting). *Common:* Blood creatinine increase; weight decrease (metastatic setting). ***Injury, poisoning:*** *Common:* Fall. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 08/2022

Oxaliplatin medac has been authorised France, Germany, Kazakhstan and United Kingdom

Pamifos® / Disodium Pamidronate 3 mg/ml

Qualitative and quantitative composition: Each ml sterile concentrate contains 3 mg pamidronate disodium as pamidronic acid 2,527 mg. 1 vial with 5 (10; 20; 30) ml concentrate contains 15 (30; 60; 90) mg pamidronate disodium. *Excipients:* sodium hydroxide, hydrochloric acid, water for injections. **Therapeutic indications:** Treatment of conditions associated with increased osteoclast activity: Tumour-induced hypercalcaemia; osteolytic lesions in patients with bone metastases associated with breast cancer; Multiple myeloma stage III. **Contraindications:** Hypersensitivity to pamidronate, other bisphosphonates or to any of the excipients; breast-feeding. **Posology and method of administration:** Medac Disodium Pamidronate 3 mg/ml is a sterile concentrate and must therefore always be diluted in a calcium-free infusion solution (0.9 % sodium chloride or 5 % glucose) before use. The resulting solution must be infused slowly. The infusion rate should never exceed 60 mg/hour (1 mg/min), and the concentration of pamidronate disodium in the infusion solution should not exceed 90 mg/250 ml. A dose of 90 mg must usually be administered as a 2 hour infusion in a 250 ml solution for infusion. In patients with multiple myeloma and patients with tumour induced hypercalcaemia, the infusion rate must not exceed 90 mg in 500 ml over 4 hours. To minimise local reactions at the infusion site, the cannula should be inserted carefully into a relatively large vein. Pamidronate disodium should be given under the supervision of a physician with the facilities to monitor the clinical and biochemical effects. Use only freshly prepared and clear dilutions! The safety and efficacy in children and adolescents (<18 years) have not been established. Tumour-induced hypercalcaemia: Patients must be rehydrated with 0.9% w/v sodium chloride solution before or/and during administration. The total dose of pamidronate disodium to be used for a treatment course depends on the patient's initial serum calcium levels. Initial plasma calcium level <3.0 (3.0–3.5; 3.5–4.0; >4.0) mmol/l => recommended dose: 15–30 (30–60; 60–90; 90) mg pamidronate disodium. The total dose of pamidronate disodium may be administered either in a single infusion or in multiple infusions over 2-4 consecutive days. The maximum dose per treatment course is 90 mg for both initial and repeat courses. Osteolytic lesions in multiple myeloma: 90 mg/4h every 4 weeks. Osteolytic lesions in bone metastases associated with breast cancer: 90mg/2h every 4 weeks (90mg/250ml; 45mg/h). Renal impairment: Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in case of life-threatening tumour induced hypercalcaemia where the benefit outweighs the potential risk. Dose adjustment is not necessary in mild (creatinine clearance 61-90 mL/min) to moderate renal impairment (creatinine clearance 30-60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20-22 mg/h). Pregnancy: Pamidronate should not be administered to pregnant women except in cases of life-threatening hypercalcaemia. Patients treated with Pamifos 3 mg/ml should be given the package leaflet and the patient reminder card. **Undesirable effects:** Adverse reactions to pamidronate disodium are usually mild and transient. The most common adverse reactions are asymptomatic hypocalcaemia and fever (an increase in body temperature of 1-2°C), typically occurring within the first 48 hours of infusion. Fever usually resolves spontaneously. ***Infections:*** *Very rare:* reactivation of herpes simplex, herpes zoster. ***Blood, lymphatic system:*** *Common:* anaemia, thrombocytopenia, lymphocytopenia; *very rare:* leukopenia. ***Immune system:*** *Uncommon:* allergic reactions including anaphylactoid reactions, bronchospasm/dyspnoea, Quincke's (angioneurotic) oedema; *very rare*: anaphylactic shock. ***Metabolism, nutrition:*** *Very common:* hypocalcaemia, hypophosphataemia; *common:* hypokalaemia, hypomagnesaemia; *very rare:* hyperkalaemia, hypernatraemia. ***Nervous system:*** *Common:* symptomatic hypocalcaemia (paraesthesia, tetany), headache, insomnia, somnolence; *uncommon:* seizures, agitation, dizziness, lethargy; *very rare:* confusion, visual hallucinations. ***Eyes:*** *Common:* conjunctivitis*; uncommon:* uveitis (iritis, iridocyclitis); *very rare:* scleritis, episcleritis, xanthopsia; *frequency not known:* orbital inflammation. ***Cardiac*** *Very rare:* left ventricular failure (dyspnoea, pulmonary oedema), congestive heart failure (oedema) due to fluid overload; *frequency not known:* atrial fibrillation. ***Vascular:*** *Common:* hypertension; *uncommon:* hypotension. ***Respiratory:*** *Very rare:* acute respiratory distress syndrome, interstitial lung disease. ***Gastrointestinal:*** *Common:* nausea, vomiting*,* anorexia, abdominal pain, diarrhoea, constipation, gastritis; *uncommon:* dyspepsia. ***Skin, subcutaneous tissue****: Common:* rash; *uncommon:* pruritus. ***Musculoskeletal, connective tissue:*** *Common:* transient bone pain, arthralgia, myalgia; *uncommon:* muscle cramp, osteonecrosis; *rare:* atypical subtrochanteric and diaphyseal femoral fractures; *very rare:* osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction); *frequency not known:* osteonecrosis of the jaw. ***Renal, urinary:*** *Uncommon:* acute renal failure; *rare:* focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome; *very rare:* deterioration of pre-existing renal disease, haematuria, renal tubular disorder, tubulointerstitial nephritis, glomerulonephropathy. ***General disorders, administration site conditions:*** *Very common:* fever and influenza like symptoms sometimes accompanied by malaise, rigors, fatigue and flushes*; common:* reactions at the infusion site (pain, redness, swelling, induration, phlebitis, thrombophlebitis), general body pain. ***Investigations:*** *Common:* increase in serum creatinine; *uncommon:* abnormal liver function tests, increase in serum urea*.* **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 12/2021

Authorised in the following countries: Czech Republic, Denmark, Germany, Finland, Netherlands, Pakistan, Slovakia, Sweden, Ukraine and United Kingdom

Pemetrexed medac 100 mg/ 500 mg/ 1.000 mg powder for concentrate for solution for infusion
Qualitative and quantitative composition: Each vial contains 100 mg/ 500 mg/ 1.000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate). *Excipients:* Mannitol (E421), hydrochloric acid, sodium hydroxide (approximately 11mg/ 54mg/ 108mg) sodium. **Therapeutic indications:** In combination with cisplatin for the treatment of unresectable malignant pleural mesothelioma. In combination with cisplatin for first line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. As monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology when disease has not progressed immediately following platinum-based chemotherapy. As monotherapy for the second line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. **Posology and method of administration:** Pemetrexed should be administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; breast-feeding; concomitant yellow fever vaccine. **Undesirable effects:** *Infections, infestations:* Very commonly infection, pharyngitis. Commonly sepsis, in some cases fatal. Very rarely Dermohypodermitis. *Blood, lymphatic system:* Very commonly neutropenia, leukopenia, haemoglobin decreased. Commonly febrile neutropenia, platelet count decreased. Uncommonly pancytopenia. Rarely autoimmune hemolytic anemia. *Immune system:* Commonly hypersensitivity. Rarely anaphylactic shock. *Metabolism, nutrition:* Commonly dehydration. *Nervous system:* Commonly taste disorder, peripheral motor or sensory neuropathy, dizziness. Uncommonly cerebrovascular accident, ischaemic stroke, hemorrhage intracranial. *Eye:* Commonly conjunctivitis, dry eye, lacrimation increased, keratoconjunctivitis sicca, eyelid oedema, ocular surface disease. *Cardiac:* Commonly cardiac failure, arrhythmia. Uncommonly angina, myocardial infarction, coronary artery disease, arrhythmia supraventricular. *Vascular:* Uncommonly peripheral ischemia leading to extremity necrosis. *Respiratory, thoracic, mediastinal:* Uncommonly pulmonary embolism, interstitial pneumonitis with respiratory insufficiency, in some cases fatal. *Gastrointestinal:* Very commonly stomatitis, anorexia, vomiting, diarrhoea, nausea. Commonly dyspepsia, constipation, abdominal pain. Uncommonly rectal or gastrointestinal hemorrhage, intestinal perforation, oesophagitis, colitis. *Hepatobiliary:* Commonly alanine aminotransferase or aspartate aminotransferase increased. Rarely hepatitis. *Skin, subcutaneous tissue:* Very commonly rash, skin exfoliation. Commonly hyperpigmentation, pruritus, erythema multiforme, alopecia, urticaria. Rarely erythema. Very rarely Stevens-Johnson syndrome, toxic epidermal necrolysis (in some cases fatal), pemphigoid, dermatitis bullous, acquired epidermolysis bullosa, erythematous oedema, pseudocellulitis, dermatitis, eczema, prurigo. *Renal, urinary:* Very commonly creatinine clearance decreased, blood creatinine increased. Commonly renal failure, glomerular filtration rate decreased. Nephrogenic diabetes insipidus, renal tubular necrosis (frequency unknown). *General:* Very commonly fatigue. Commonly pyrexia, pain, oedema, chest pain, mucosal inflammation. *Investigations:* Commonly gamma-glutamyltransferase increased. *Injury:* Uncommonly radiation oesophagitis, radiation pneumonitis. Rarely recall phenomenon. **Legal classification**: POM (prescription only medicine). **Marketing authorisation number:** EU/1/15/1038/001-003 **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 08/2022
Pemetrexed medac has been authorized in all countries of the EU.

Topotecan medac 1 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: 1 ml concentrate for solution for infusion contains 1 mg topotecan (as hydrochloride). *Excipients:* Water for injections, hydrochloric acid, sodium hydroxide. **Therapeutic indications:** Monotherapy treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy. Monotherapy treatment of patients with relapsed small cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate. In combination with cisplatin for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease; patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination. **Posology and method of administration:** Confined to units specialised in the administration of cytotoxic chemotherapy section. Topotecan must be diluted before use. *Ovarian and small cell lung cancer:* The recommended dose of topotecan is 1.5 mg/m²/day administered by intravenous infusion over 30 minutes daily for five consecutive days with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression. *Cervical carcinoma:* The recommended dose of topotecan is 0.75 mg/m²/day administered as 30-minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m²/day and following the topotecan dose. Treatment schedule is repeated every 21 days for six courses or until progressive disease. For details see summary of product characteristics. **Contraindications:** Severe hypersensitivity to the active substance or to any of the excipients; breast-feeding; severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count of < 100 x 10^9/l. **Undesirable effects:** The dose limiting toxicity of topotecan monotherapy is haematological. Toxicity was predictable and reversible. There were no signs of cumulative haematological or non-haematological toxicity. *Infections, infestations:* Very commonly infection. Commonly sepsis, fatalities have been reported. *Blood, lymphatic system*: Very commonly febrile neutropenia, neutropenia (severe in 77% of patients), thrombocytopenia (severe in 25% of patients), anaemia (moderate to severe in 37% of patients), leucopenia; commonly pancytopenia. Severe bleeding (frequency not known). *Immune system:* Commonly hypersensitivity reaction including rash, rarely anaphylactic reaction, angioedema, urticaria. *Metabolism, nutrition:* Very commonly anorexia (which may be severe). *Respiratory, thoracic, mediastinal:* Rarely interstitial lung disease (some cases have been fatal). *Gastrointestinal:* Very commonly nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain, mucositis. Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia. Gastrointestinal perforation (frequency not known). *Hepatobiliary:* Commonly hyperbilirubinemia. *Skin and subcutaneous tissue:* Very commonly alopecia, commonly pruritus. *General; administration site:* Very commonly pyrexia, asthenia, fatigue; commonly malaise. Very rarely extravasation, generally with mild reactions. Mucosal inflammation (frequency not known). Additional adverse events were seen when topotecan was given in combination with cisplatin (see SPC of cisplatin). **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH, Theaterstr. 6, 22880 Wedel, Germany. **Date of revision of text:** 01/2023

Topotecan medac has been authorised in Germany, Pakistan, Poland and Slovak Republic

Trecondi® 1 g / 5 g powder for solution for infusion

Qualitative and quantitative composition: One vial Trecondi 1 g (5 g) powder for solution for infusion contains 1 g (5 g) of treosulfan. When reconstituted, 1 mL of the solution for infusion contains 50 mg treosulfan. **Therapeutic indications:** Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients and in paediatric patients older than one month with malignant and non-malignant diseases. **Posology and method of administration:** Administration should be supervised by a physician experienced in conditioning treatment followed by alloHSCT. A*dults with malignant disease:* Treosulfan is given in combination with fludarabine. Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²; Treosulfan should be administered before fludarabine. *Adults with non malignant disease*: Treosulfan is given in combination with fludarabine with or without thiotepa. Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 42 g/m²; Treosulfan should be administered before fludarabine. *Paediatric population:* Treosulfan is given in combination with fludarabine, with or without thiotepa. **Contraindications:** Hypersensitivity to the active substance; active non-controlled infectious disease; severe concomitant cardiac, lung, liver, and renal impairment; Fanconi anaemia and other DNA breakage repair disorders; pregnancy; administration of live vaccine. **Undesirable effects:** *Infections, infestations:* Very commonly infections (bacterial, viral, fungal). Commonly **s**epsis. Septic shock. *Neoplasms:* Treatment related second malignancy. *Blood, lymphatic system:* Very commonly myelosuppression, pancytopenia, febrile neutropenia. *Immune system:* Commonly hypersensitivity. *Metabolism and nutrition:* Commonly decreased appetite. Uncommonly glucose tolerance impaired including hyperglycaemia and hypoglycaemia. Acidosis, alkalosis, electrolyte imbalance, hypomagnesaemia. *Psychiatric:* Commonly insomnia. Uncommonly confusional state. *Nervous system:* Commonly headache, dizziness. Uncommonly intracranial haemorrhage, peripheral sensory neuropathy. Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia, seizure. *Eye:* Dry eye, conjunctival haemorrhage. *Ear:* Uncommonly vertigo. *Cardiac:* Commonly cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia). Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion. *Vascular:* Commonly hypertension, hypotension, flushing. Uncommon haematoma. Embolism, capillary leak syndrome. *Respiratory, thoracic, mediastinal:* Commonly dyspnoea, epistaxis, oropharyngeal pain. Uncommonly pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, hiccups. Laryngeal pain, cough, dysphonia, hypoxia. *Gastrointestinal:* Very commonly stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain. Commonly oral pain, gastritis, dyspepsia, constipation, dysphagia, oesophageal or gastrointestinal pain, anal inflammation. Uncommonly mouth haemorrhage, abdominal distension, dry mouth. Gastric haemorrhage, neutropenic colitis, oesophagitis, proctitis, gingival pain. *Hepatobiliary:* Very commonly hepatotoxicity. Uncommonly veno-occlusive liver disease. Hepatomegaly. *Skin, subcutaneous tissue:* Very commonly pruritus, alopecia. Commonly (maculo-papular) rash, purpura, erythema, urticaria, palmar plantar erythrodysaesthesia syndrome, dermatitis exfoliative, pain of skin, skin hyperpigmentation. Uncommonly erythema multiforme, dermatitis acneiform, dry skin. Skin necrosis or ulcer, dermatitis, dermatitis bullous, dermatitis diaper. *Musculoskeletal and connective tissue:* Commonly pain in extremity, back pain, bone pain, arthralgia. Uncommonly myalgia. *Renal, urinary:* Commonly acute kidney injury, haematuria. Uncommonly urinary tract pain. Renal failure, haemorrhagic or noninfective cystitis, dysuria. *Reproductive system:* Scrotal erythema, penile pain. *General, administration site:* Very commonly asthenic conditions (fatigue, asthenia, lethargy), pyrexia. Commonly oedema, chills. Uncommonly non cardiac chest pain, pain, face oedema. *Investigations:* Very commonly blood bilirubin increased, ALT increased. Commonly AST increased, γGT increased, C-reactive protein increased, weight decreased, weight increased. Uncommonly blood alkaline phosphatase increased. Blood lactate dehydrogenase (LDH) increased. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 11/2023

Trecondi has been authorised in all countries of the EU as well as in Belarus, Iceland, Kazakhstan, Norway, Liechtenstein, Russia, Switzerland (OpoPharma AG), United Kingdom and Ukraine

Navirel® / Vinorelbine 10 mg/ml concentrate for solution for infusion

Qualitative and quantitative composition: Each 1 ml (5 ml) vial contains a total content of vinorelbine (as tartrate) of 10 mg (50 mg). Excipients: Water for injections. **Therapeutic indications:** *All countries except UK:* As single agent in patients with metastatic breast cancer (stage 4), where treatment with anthracycline- and taxane containing chemotherapy has failed or is not appropriate. Non-small cell lung cancer (stage 3 or 4). *UK:* As single agent or in combination for first line treatment of stage 3 or 4 non small cell lung cancer. Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. **Posology and method of administration:** Strictly intravenous administration after appropriate dilution. Intrathecal administration of vinorelbine may be fatal. Vinorelbine is usually given at 25-30 mg/m² body surface area once weekly. In combination with other cytostatic agents the exact dose should be taken from the treatment protocol. Vinorelbine may be administered by slow bolus (6-10 minutes) after dilution in 20-50 ml of sodium chloride 0.9% solution for injection or in 5% glucose solution for injection or by a short infusion (20-30 minutes) after dilution in 125 ml of sodium chloride 0.9% solution for injection or in 5% glucose solution for injection. Administration should always be followed by a sodium chloride 9 mg/ml (0.9 %) infusion with at least 250 ml to flush the vein. Maximum tolerated dose per administration: 35.4 mg/m² body surface area; maximum total dose per administration: 60 mg. Safety and efficacy in children have not been established. **Contraindications:** Hypersensitivity to active substance or other vinca alkaloids, or to any of the excipients; neutrophil count < 1,500/mm³ or severe current or recent infection (within the last 2 weeks); thrombocyte count below 100,000/mm³; severe hepatic impairment not related to the tumoural process; in combination with yellow fever vaccine; pregnancy, lactation. **Undesirable effects:** *Infections, infestations:* Commonly infection bacterial, viral or fungal at different localisation (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment. Uncommonly severe sepsis with other visceral failure, septicaemia. Very rarely septicaemia complicated; septicaemia fatal. Neutropenic sepsis with potential fatal outcome, frequency not known. *Blood, lymphatic system:* Very commonly bone marrow depression resulting mainly in neutropenia, reversible within 5 to 7 days and non-cumulative over time, anaemia. Commonly thrombocytopenia, seldom severe. Febrile neutropenia, pancytopenia, frequency not known. *Immune system:* Commonly allergic reactions (skin reactions, respiratory reactions). Systemic allergic reactions (anaphylactic reaction or shock, anaphylactoid reaction, angioedema), frequency unknown. *Endocrine:* Inappropriate antidiuretic hormone secretion (SIADH), frequency not known. *Metabolism, nutrition:* Rarely severe hyponatraemia. Anorexia, frequency not known. *Nervous system:* Very commonly neurological disorders including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy. Uncommonly severe paraesthesia with sensory and motor symptoms. These effects are generally reversible. Very rarely Guillain Barré syndrome. Posterior reversible encephalopathy syndrome, frequency not known. *Cardiac:* Rarely ischaemic heart diseases like angina pectoris, transitory electrocardiogram changes, myocardial infarction, sometimes fatal. Very rarely tachycardia, palpitation and heart rhythm disorders. *Vascular:* Uncommonly hypotension, hypertension, flushing and peripheral coldness. Rarely severe hypotension, collapse. *Respiratory, thoracic, mediastinal:* Uncommonly dyspnoea, bronchospasm. Rarely interstitial lung disease, sometimes fatal. Very rarely respiratory insufficiency. Pulmonary embolism, frequency not known. *Gastrointestinal:* Very commonly constipation, which rarely progresses to paralytic ileus; nausea and vomiting, antiemetic therapy may reduce their occurrence; stomatitis, oesophagitis. Commonly diarrhoea. Rarely paralytic ileus; treatment may be resumed after recovery of normal bowel mobility; pancreatitis. *Hepatobiliary:* Very commonly transient elevations of liver function tests without clinical symptoms (total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase increased). *Skin, subcutaneous tissues:* Very commonly alopecia usually mild in nature. Rarely generalised cutaneous reactions. Palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation (serpentine supravenous hyperpigmentation), frequency unknown. *Musculoskeletal, connective tissues*: Commonly myalgia, arthralgia, jaw pain. *Renal, urinary:* Commonly creatinine increased. *General, administration site conditions:* Very commonly asthenia, fatigue, fever, pain in different locations including chest pain and pain at the tumour site. Reactions at the injection site may include erythema, burning pain, vein discolouration and local phlebitis. Rarely injection site necrosis (proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects). In combined chemotherapy of vinorelbine with other antineoplastic medicinal products it has to be considered, that the listed undesirable effect can occur more frequently and more severe than those undesirable effects observed during and after monotherapy. **Legal classification**: POM (prescription only medicine). **Marketing authorisation holder:** medac GmbH Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text**: 02/2023

Registered in the following countries: Czech Republic, Denmark, Germany, The Netherlands, Norway, Poland, Portugal, Slovakia, Sweden, Ukraine and United Kingdom

Zoledronic acid medac 4 mg/100 ml solution for infusion

Qualitative and quantitative composition: One bottle with 100 ml solution contains 4 mg zoledronic acid (as monohydrate). One ml solution contains 0.04 mg zoledronic acid (as monohydrate). *Excipients:* Mannitol, sodium citrate, water for injections. **Therapeutic indications:** Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone; treatment of tumour-induced hypercalcaemia (TIH) in adult patients. **Posology and method of administration:** Patients treated with Zoledronic acid medac should be given the package leaflet and the patient reminder card. The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks. Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid. Zoledronic acid medac 4 mg/5 ml concentrate, further diluted in 100 ml, should be given as a single intravenous infusion in no less than 15 minutes. In patients with mild to moderate renal impairment, reduced doses are recommended. Patients must be maintained well hydrated prior to and following administration. **Contraindications:** Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients; breast-feeding. **Undesirable effects:** *Blood, lymphatic system:* Commonly anaemia. Uncommonly thrombocytopenia, leukocytopenia. Rarely pancytopenia. *Immune system:* Uncommonly hypersensitivity reaction. Rarely angioneurotic oedema. *Psychiatric:* Uncommonly anxiety, sleep disturbance. Rarely confusion. *Nervous system:* Commonly headache. Uncommonly dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence. Very rarely convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia). *Eye:* Commonly conjunctivitis. Uncommonly blurred vision, scleritis, orbital inflammation. Rarely uveitis. Very rarely episcleritis. *Cardiac:* Uncommonly hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse. Rarely bradycardia, cardiac arrhythmia (secondary to hypocalcaemia). *Respiratory, thoracic, mediastinal:* Uncommonly dyspnoea, cough, bronchoconstriction. Rarely interstitial lung disease. *Gastrointestinal:* Commonly nausea, vomiting, decreased appetite. Uncommonly diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth. *Skin, subcutaneous tissue:* Uncommonly pruritus, rash (including erythematous and macular rash), increased sweating. *Musculoskeletal, connective tissue:* Commonly bone pain, myalgia, arthralgia, generalised pain. Uncommonly muscle spasms, osteonecrosis of the jaws. Rarely atypical subtrochanteric and diaphyseal femoral fractures. Very rarely osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip. *Renal, urinary:* Commonly renal impairment. Uncommonly acute renal failure, haematuria, proteinuria. Rarely acquired Fanconi syndrome. *General, administration site:* Commonly fever, flu-like syndrome (including fatigue, rigors, malaise and flushing). Uncommonly asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria. Rarely arthritis and joint swelling as a symptom of acute phase reaction. *Investigations:* Very commonly hypophosphataemia. Commonly blood creatinine and blood urea increased, hypocalcaemia. Uncommonly hypomagnesaemia, hypokalaemia. Rarely hyperkalaemia, hypernatraemia. **Legal classification**: POM (prescription only medicine). **Marketing authorisation numbers:** EU/1/12/779/004-005 **Marketing authorisation holder:** medac GmbH, Theaterstraße 6; 22880 Wedel, Germany. **Date of revision of text** 09/2020

Zoledronic acid medac has been authorised in all countries of the EU as well as in Iceland, Norway and Liechtenstein