

From

Date

(M.D.)

(name)

(address)

(telephone #)

(fax #)

Baxter Oncology GmbH
Gabriele Meuer - Assistant, Global Medical Marketing
Daimlerstrasse 40
D-60314 Frankfurt am Main
GERMANY

Ladies and Gentlemen:

This letter requests a limited supply of

(name of the product)

in order to meet the needs of one of my patients,

(name of patient)

This patient has

(Give description of disease and why product is needed, including whether any effective and approved treatment is available in the USA. If this is a request for extended use of medication, please document why continued therapy is desired.)

The product will be used exclusively for this patient in order to treat his/her condition.

This patient has affirmed in writing to me and I independently affirm that the product will be for his/her own use. The patient's written statement is attached. This patient has specifically requested this therapy and has given his/her written consent. The product will not be in any way distributed for commercial use or used for any other patients.

As the attending physician responsible for treatment with this product, I will return to Baxter Oncology any unused supplies of this drug, if administration to this patient is discontinued or terminated before the supply is exhausted.

I have learned of this product from reports in the scientific literature. I am aware that the product is currently not approved by the US Food and Drug Administration for any drug use in the United States. I assume the responsibility and liability for the administration of the product to this patient.

I promise not to publish or otherwise disseminate information about this patient's experience with the product without Baxter Oncology's prior approval. However, I will provide Baxter Oncology with a report on this patient's experience with this product.

Sincerely,

(Signature)

(Name)

(License Number)

Baxter Oncology

Miltex[®]: Questionnaire on Compassionate Use

Treating Physician

Title, Name: _____
Hospital/Department: _____
Address: _____

Patient:

Initials (first/last name) ___/___ Age (years): Sex (m/f):

Diagnosis of Systemic Disease:

Type of systemic disease (e.g. breast cancer):

first diagnosed in (Month/Year):

Diagnosis and prior Treatment of Cutaneous Disease

Type of cutaneous disease (e.g. breast cancer skin metastases):

first diagnosed in (Month/Year):

Prior Therapy: no yes if yes, please specify:

Current Status of Cutaneous Disease

Site(s) of skin involvement:

Total area to be treated:

Approx. No. of skin lesions: Approx. diameter of largest skin lesion[cm]:

Confluent lesions: yes no Ulcerated lesions: yes no

Additional Notes:

Miltex[®] Therapy

Start with Miltex[®] Therapy: / / / (day/month/year)

Miltex[®] Dosage: drops per 10 cm² treated area:

Frequency of Application: once daily twice daily other; please specify:

Response Evaluation

Please define a **marker lesion** within the area to be treated and evaluate the response according to the following criteria: **CR**: complete disappearance of lesions within treated area; **PR**: $\geq 50\%$ decrease in lesions within treated area; **NC**: No change or $< 50\%$ decrease or $< 25\%$ increase in lesions within treated area; **PD**: $>25\%$ increase of a lesion in treated area or new lesions within treated area. Please indicate also the longitudinal and transverse diameter of the marker lesion.

Evaluation on (day/month/year)	Marker Lesion		Response
	longitudal diameter [cm]	transverse diameter [cm]	
			baseline
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>
			CR <input type="checkbox"/> PR <input type="checkbox"/> NC <input type="checkbox"/> PD <input type="checkbox"/>

Concomitant Therapy: no yes . If yes, please specify (e.g. drug, treatment duration,...):

Adverse Drug Reactions

Type	Intensity	Date of first occurrence (day/month/year)
	mild <input type="checkbox"/> moderate <input type="checkbox"/> severe <input type="checkbox"/>	
	mild <input type="checkbox"/> moderate <input type="checkbox"/> severe <input type="checkbox"/>	
	mild <input type="checkbox"/> moderate <input type="checkbox"/> severe <input type="checkbox"/>	

Compassionate Use of Miltex[®]: Patient's Questionnaire

(To be filled in by physician according to information given by patient)

Dear Patient:

You are receiving a treatment with Miltex[®]. In addition to the evaluation of the treatment by your doctor, your personal judgement and experience with this treatment is of very high importance. For this reason, you are kindly asked to answer the following questions, each time you are visiting your doctor. For each visit a new questionnaire will be used. Please feel free to give additional comments. Thank you very much!

Date:	___/___/___	(day/month/year)
Please enter your initials:	___/___	(first name/last name)
Please enter your age (years):	Please indicate your sex: <input type="checkbox"/> male <input type="checkbox"/> female	

Who applied Miltex [®] to your skin?	<input type="checkbox"/> myself	<input type="checkbox"/> myself and other person	<input type="checkbox"/> other person	
How easy was the application of Miltex [®] ?	<input type="checkbox"/> very easy	<input type="checkbox"/> easy	<input type="checkbox"/> complicated	<input type="checkbox"/> very complicated
Do you think the treatment with Miltex [®] helps you?	<input type="checkbox"/> very much	<input type="checkbox"/> much	<input type="checkbox"/> a little	<input type="checkbox"/> no
What is your general judgement of Miltex [®] efficacy?	<input type="checkbox"/> very good	<input type="checkbox"/> good	<input type="checkbox"/> moderate	<input type="checkbox"/> bad
What is your general judgement of Miltex [®] tolerability?	<input type="checkbox"/> very good	<input type="checkbox"/> good	<input type="checkbox"/> moderate	<input type="checkbox"/> bad

If you have any comments or suggestions, please enter them here:

Information about Miltex[®]

A) There are no ongoing clinical trials in North America. Until now we have no partner to work with this product in the United States and our conversations with the FDA have been stopped for the moment. We have supplied some bottles of Miltex[®] as part of a compassionate use program, based on named patients. That means that the request must come in written form by the doctor/physician him/herself. In this letter he/she should describe the individual patient, including the following information:

- patient's initials
- indication
- history of disease, short description (first diagnosis, prior treatments...)
- reason why Miltex[®] should be applied
- total surface area to be treated in cm²
- requested amount of medication (no of bottles)
- doctor's signature and hospital/clinic affiliation.

The attached documents will give us the information about the ongoing treatment and should be sent after the initial 8 weeks of treatment with Miltex[®], when medication will continued, or if treatment has been stopped.

Officially there are no trials running with this drug. Probably in some countries the doctor himself decides to register the cases treated with Miltex[®] to present his/her results at a later date, but it is only under practical use.

B) Until now some trials have been performed, mainly in Europe. Clinical studies were conducted after 1986 concerning cutaneous metastases of breast cancer with the topical application of the drug. Most of the studies were conducted as multicentric trials.

Two phase I studies on topical applied miltefosine have been conducted involving dose escalation schedules: the maximum tolerated concentration and dose were established.

Phase II clinical studies: The 6% solution of miltefosine was used throughout the phase II studies of Miltex[®], and in the majority of studies a modification of the posology (standard 2 drops per 10 cm²) was only anticipated in case of poor tolerability.

There were 9 phase II clinical trials performed, which were used as a basis of an integrated meta-analysis. The global response rate assessed by the best local response and its corresponding confidence intervals is 27%, in patients heavily pretreated and with different lesions characteristics (also ulcerated lesions, deep skin infiltrations...).

Due the fact that Miltex[®] is already available in several markets, additional phase II clinical trials have been performed, with higher response rates due a better selection of the treated patients: response rates around 40%.

Phase III clinical study: A randomized clinical study comparing Miltex[®] with placebo has been performed in UK. The data was presented in abstract form at ASCO 99 (American Society of Clinical Oncology), Atlanta and was published as a full article in the Journal of Clinical Oncology (JCO) in November 2001. Response Rate to Miltex[®] was 42.1% compared to a response rate of 4.2% respectively for placebo.

- C) Taken into account that Miltex[®] is used for topical treatment, the skin is the main organ which will be affected by its application.

Therefore, local skin reactions such as skin redness, itching, dry skin, scaling, tension and burning (especially in ulcerated lesions) are commonly observed after application of Miltex[®].

In exceptional cases more severe local reactions (like dermatitis, atrophy, ulceration or necrotizing lesions) may require interruption or discontinuation of treatment.

Application

The standard dose of study medication is 2 drops/10 cm². A margin of approximately 3 cm around the visible skin infiltration should be included in the treatment area.

During the first week of treatment, the standard dose will be applied once daily:

If no important toxicity is observed, the standard dose will be applied twice daily from the second week of treatment. If treatment is not well tolerated, 50% of the standard dose (1 drop/10 cm²) should be applied twice daily (total daily dose maintained).

After washing the calculated amount of the medication will be dropped onto the skin to be treated and distributed by gentle massage with a glove-protected hand (Note : although it is not necessary to use sterile gloves, it is recommended that gloves should be used only once). Larger amounts of solution may require sequential application of smaller fractions. The solution should be taken up by the skin in about 1-2 minutes. Thereafter, if necessary, the treated area can be covered by gauze or other non-occlusive medical dressing.

Local skin reactions to Miltex[®], including dry skin, pruritus, and desquamation may be palliated by additional application of an inert moisturising or fat cream (e.g.: E45 or Vaseline). A period of 2-3 hours should be allowed between application of the study medication and the application of the inert cream.

Depending on the type and severity of symptoms, either a reduction of drops or a delay of treatment (up to 1 week) may be allowed until improvement or resolution of the symptom.

- D) The therapy of skin metastases or local recurrences in women with breast cancer is often difficult, particularly if surgical intervention is not possible and the tumor does not respond to conventional radio-, chemo- or hormone therapy. Miltex[®], active constituent miltefosine (hexadecylphosphocholine), represents a new therapeutic option for the topical treatment of these problematical skin metastases. Miltex[®] differs from conventional cytostatic agents because of his unique mode of action attacking the cell membrane and the associated cell signaling mechanisms.

Response to Miltex[®] treatment varies. Superficial growth patterns (small nodular up to 1 cm in diameter, flat) which require less depth of Miltex[®] penetration, respond to Miltex[®] significantly better. Sometimes you will find a regression of the skin lesions, in other cases a stabilization. In cases of open wounds the recommendation is to apply the drug around the border until the lesion has cured.

Patient Information on the use of Miltex®

Dear Patient,

Your doctor has prescribed MILTEX® for the treatment of your skin lesions. Here is some information and advice about how to use this product.

What is Miltex® for?

Miltex® is the brand name for miltefosine solution. It is a topical treatment applied directly to your skin lesions and it is not to be swallowed or used in any other way.

How much Miltex® should you use?

The amount of Miltex® used is 2 drops for every 10 square centimetres (1.5 square inches) of skin area.

Do not use more than 5 ml (200 drops, about half a bottle) of Miltex® per day. Only if your doctor has told you, you can exceed this maximal recommended dose.

How often should you use Miltex®?

First week:	Once a day
Following weeks:	Twice a day once in the morning and once in the evening

How long should you use Miltex®?

If there are no problems, you should use Miltex® for at least 8 weeks. Your doctor will monitor the response of the lesions and indicate how long you have to continue the treatment. If your skin lesions do not improve, consult your doctor.

Dose modification in case of local reactions:

Usually this treatment does not cause problems, but the application of Miltex® can give you some local side effects like skin irritation, itching, redness, dryness.

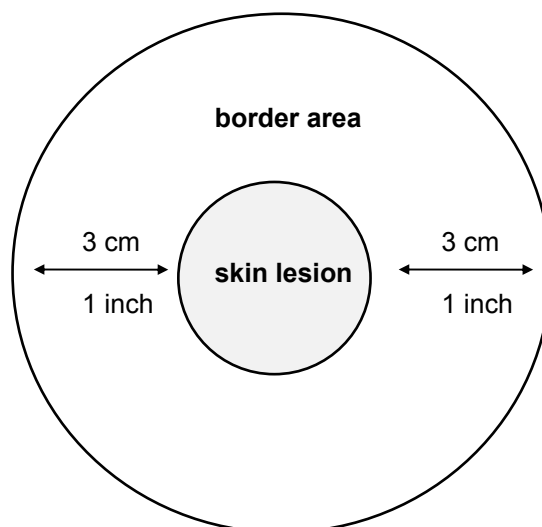
If these occur, notify your doctor. He will

reduce the daily dose to 50%, maintaining two applications per day, (i.e. if you are applying 10 drops in the morning and 10 drops in the evening, in the next application you will apply 5 drops in the morning and 5 in the evening).

If the reduced dose still causes problems, you could also interrupt the treatment temporarily.

Area to be treated

The surface to be treated must be the affected skin area and a border area of 3 cm (1 inch) around it.



Calculation of the amount of Miltex®

After you have measured the diameter of the skin lesion, the following table will help you work out how much Miltex® to apply.

Diameter of the skin lesion	Maximum number of drops per application for the lesion and the border
1 cm	8 drops
2 cm	10 drops
3 cm	13 drops
4 cm	16 drops
5 cm	19 drops
6 cm	23 drops
7 cm	27 drops
8 cm	31 drops
9 cm	35 drops
10 cm	40 drops

Practical aspects of topical administration



To apply Miltex® put on the disposable gloves and remove any old dressings from the affected skin area. Clean the area to be treated with physiologic saline (salt water) or bottled water.

Open the Miltex® bottle as shown in the illustration.

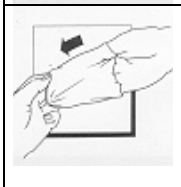


Apply the correct number of drops of Miltex® onto the affected skin area to be treated including the border area.



Gently rub the liquid into the skin with circular movements.

Leave the affected area uncovered until Miltex® is completely absorbed.



Take the used dressing in your gloved fingers. Remove the glove carefully to include the dressing as shown in the illustration.

Be careful to avoid any contact of non-affected skin with Miltex®. The gloves and the dressings can be disposed of with the usual household waste.

Do not wash the skin for several hours after using Miltex®.

If the area is ulcerated the treated area could be covered with gauze or with non occlusive dressings. In case of large areas being affected, the use of cotton underwear could be a good choice. The used underwear can be washed afterwards as usual.

When there are local skin problems like skin dryness, the use of a moisturized inert cream is recommended.

**Avoid contact with the eyes and mucous membranes!
In case of accidental contact copious washing with water is recommended.**

FDA Requirements

According to the FDA requirements every doctor, who intends to import Miltex[®], needs to send us the following information via written notice on his/her letterhead:

1. written affirmation of the drug's intended use (commercial or personal use).
If personal, please indicate patient's identification
2. total amount of medication to be imported, and
3. written affirmation that it is not possible to obtain this drug in the U.S.
4. Patient's written affirmation that the product is intended for her own use.