ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Liposome–encapsulated doxorubicin–citrate complex corresponding to 50 mg doxorubicin hydrochloride (HCl).

Excipient(s) with known effect: The reconstituted medicinal product contains approximately 108 mg sodium for a 50 mg doxorubicin HCl dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder, dispersion and solvent for concentrate for dispersion for infusion

Myocet is supplied as a three-vial system:
Myocet doxorubicin HCl is a red lyophilised powder.
Myocet liposomes is a white to off-white, opaque and homogeneous dispersion.
Myocet buffer is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myocet, in combination with cyclophosphamide, is indicated for the first line treatment of metastatic breast cancer in adult women.

4.2 Posology and method of administration

The use of Myocet should be confined to units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy.

Posology
When Myocet is administered in combination with cyclophosphamide (600 mg/m^2) the initial recommended dose of Myocet is 60-75 mg/m^2 every three weeks.

Older people
Safety and efficacy of Myocet have been assessed in 61 patients with metastatic breast cancer, age 65 and over. Data from randomised controlled clinical trials show that the efficacy and cardiac safety of Myocet in this population was comparable to that observed in patients less than 65 years old.

Patients with hepatic impairment
As metabolism and excretion of doxorubicin occurs primarily by the hepatobiliary route, evaluation of hepatobiliary function should be performed before and during therapy with Myocet.
Based on limited data in patients with liver metastases, it is recommended that the initial dose of Myocet is reduced in accordance with the following table

Liver function tests	Dose
Bilirubin < ULN and normal AST	Standard dose of 60 - 75mg/m^2
Bilirubin < ULN and raised AST	Consider a 25% dose reduction

Liver function tests	Dose
Bilirubin > ULN but < 50 µmol/l	50% dose reduction
Bilirubin > 50 µmol/l	75% dose reduction

If possible, Myocet should be avoided in patients with bilirubin > 50 µmol/l as the recommendation is based mainly on extrapolations.

For dose reductions due to other toxicity, see section 4.4.

Patients with renal impairment
Doxorubicin is metabolised largely by the liver and excreted in the bile. Therefore dose modification is not required for patients with renal function impairment.

Paediatric population
The safety and efficacy of Myocet in children aged up to 17 years has not been established. No data are available.

Method of administration
Myocet must be reconstituted and further diluted prior to administration. A final concentration of between 0.4 mg/ml to 1.2 mg/ml doxorubicin HCl, is required. Myocet is administered by intravenous infusion over a period of 1 hour.

Myocet must not be administered by the intramuscular or subcutaneous route or as a bolus injection.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Myelosuppression
Therapy with Myocet causes myelosuppression. Myocet should not be administered to individuals with absolute neutrophil counts (ANC) lower than 1,500 cells/µl or platelets less than 100,000/µl prior to the next cycle. Careful haematological monitoring (including white blood cell and platelet count, and haemoglobin) should be performed during therapy with Myocet.
A meta-analysis showed a statistically significant lower rate of grade 4 neutropenia (RR = 0.82, p=0.005) in patients treated with Myocet versus conventional doxorubicin. However, no significant differences were identified in the occurrence of anaemia, thrombocytopenia and episodes of neutropenic fever.

Haematological as well as other toxicity may require dose reductions or delays. The following dosage modifications are recommended during therapy and should be performed in parallel for both Myocet and cyclophosphamide. Dosing subsequent to a dose reduction is left to the discretion of the physician in charge of the patient.

Haematological Toxicity			
Grade	**Nadir ANC (cells/µl)**	**Nadir Platelet Count (cells/µl)**	**Modification**
1	1500 – 1900	75,000 – 150,000	None
2	1000 – Less than 1500	50,000 – Less than 75,000	None
3	500 – 999	25,000 – Less than 50,000	Wait until ANC 1500 or more and/or platelets 100,000 or more then redose at 25% dose reduction

Haematological Toxicity			
Grade	**Nadir ANC (cells/µl)**	**Nadir Platelet Count (cells/µl)**	**Modification**
4	Less than 500	Less than 25,000	Wait until ANC 1500 and/or platelets 100,000 or more then redose at 50% dose reduction

If myelotoxicity delays treatment to greater than 35 days after the first dose of the previous cycle, then consideration should be given to stopping treatment.

Mucositis		
Grade	**Symptoms**	**Modification**
1	Painless ulcers, erythema, or mild soreness.	None
2	Painful erythema, oedema or ulcers but can eat.	Wait one week and if the symptoms improve redose at 100% dose
3	Painful erythema, oedema or ulcers and cannot eat	Wait one week and if symptoms improve redose at 25% dose reduction
4	Requires parenteral or enteral support	Wait one week and if symptoms improve redose at 50% dose reduction

For dose reduction of Myocet due to liver function impairment, see section 4.2.

Cardiac toxicity

Doxorubicin and other anthracyclines can cause cardiotoxicity. The risk of toxicity rises with increasing cumulative doses of those medicinal products and is higher in individuals with a history of cardiomyopathy, or mediastinal irradiation or pre-existing cardiac disease.

Analyses of cardiotoxicity in clinical trials have shown a statistically significant reduction in cardiac events in patients treated with Myocet compared to patients treated with conventional doxorubicin at the same dose in mg. A meta-analysis showed a statistically significant lower rate of both clinical heart failure (RR = 0.20, p=0.02) and clinical and subclinical heart failure combined (RR = 0.38, p<0.0001) in patients treated with Myocet versus conventional doxorubicin. The reduced risk of cardiotoxicity has also been shown in a retrospective analysis in patients who had received prior adjuvant doxorubicin (log-rank P=0.001, Hazard Ratio=5.42).

In a phase III study in combination with cyclophosphamide (CPA) comparing Myocet (60 mg/m^2) + CPA (600 mg/m^2) versus doxorubicin (60 mg/m^2) + CPA (600 mg/m^2), 6% versus 21% of patients, respectively, developed a significant decrease in left ventricular ejection fraction (LVEF). In a phase III study comparing single-agent Myocet (75 mg/m^2) versus single-agent doxorubicin (75 mg/m^2), 12% versus 27% of patients, respectively developed a significant decrease in LVEF. The corresponding figures for congestive heart failure (CHF), which was less accurately assessed, were 0% for Myocet + CPA versus 3% for doxorubicin + CPA, and 2% for Myocet versus 8% for doxorubicin. The median lifetime cumulative dose of Myocet in combination with CPA to a cardiac event was > 1260 mg/m^2, compared to 480 mg/m^2 for doxorubicin combination with CPA.

There is no experience with Myocet in patients with a history of cardiovascular disease, e.g. myocardial infarction within 6 months prior to treatment. Thus, caution should be exercised in patients with impaired cardiac function. The cardiac function of the patients treated concomitantly with Myocet and trastuzumab must be appropriately monitored as described below.

The total dose of Myocet should also take into account any previous, or concomitant, therapy with other cardiotoxic compounds, including anthracyclines and anthraquinones.

Before initiation of Myocet therapy a measurement of left ventricular ejection fraction (LVEF) is routinely recommended, either by Multiple Gated Arteriography (MUGA) or by echocardiography.

These methods should also be applied routinely during Myocet treatment. The evaluation of left ventricular function is considered mandatory before each additional administration of Myocet once a patient exceeds a lifetime cumulative anthracycline dose of 550 mg/m^2 or whenever cardiomyopathy is suspected. If LVEF has decreased substantially from baseline e.g. by > 20 points to a final value > 50% or by > 10 points to a final value of < 50%, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage. However, the most definitive test for anthracycline myocardial injury, i.e., endomyocardial biopsy, should be considered.

All patients receiving Myocet should also routinely undergo ECG monitoring. Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for the cessation of Myocet therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity.

Congestive heart failure due to cardiomyopathy may occur suddenly, and may also be encountered after discontinuation of therapy.

Gastroinstestinal disorders
A meta-analysis showed a statistically significant lower rate of nausea/vomiting grade ≥ 3 (RR = 0.65, p=0.04) and diarrhoea grade ≥ 3(RR = 0.33, p=0.03) in patients treated with Myocet versus conventional doxorubicin.

Injection site reactions
Myocet should be considered an irritant and precautions should be taken to avoid extravasation. If extravasation occurs, the infusion should be immediately terminated. Ice may be applied to the affected area for approximately 30 minutes. Subsequently, the Myocet infusion should be restarted in a different vein than that in which the extravasation has occurred. Note that Myocet may be administered through a central or peripheral vein. In the clinical program, there were nine cases of accidental extravasation of Myocet, none of which were associated with severe skin damage, ulceration or necrosis.

Infusion associated reactions
When infused rapidly acute reactions associated with liposomal infusions have been reported. Reported symptoms have included flushing, dyspnoea, fever, facial swelling, headache, back pain, chills, tightness in the chest and throat, and/or hypotension. These acute phenomena may be avoided by using a 1-hour infusion time.

Other
For precautions regarding the use of Myocet with other medicinal products, see section 4.5.
As for other anthracyclines and doxorubicin products, radiation recall may occur in previously irradiated fields.
Efficacy and safety of Myocet in the adjuvant treatment of breast cancer have not been determined. The importance of apparent differences in tissue distribution between Myocet and conventional doxorubicin has not been elucidated with respect to long-term antitumour efficacy.

4.5 Interactions with other medicinal products and other forms of interactions

Specific medicinal product compatibility studies have not been performed with Myocet. Myocet is likely to interact with substances that are known to interact with conventional doxorubicin. Plasma levels of doxorubicin and its metabolite, doxorubicinol, may be increased when doxorubicin is administered with cyclosporin, verapamil, paclitaxel or other agents that inhibit P-glycoprotein (P-Gp). Interactions with doxorubicin have also been reported for streptozocin, phenobarbital, phenytoin and warfarin. Studies of the effect of Myocet on other substances are also lacking. However, doxorubicin may potentiate the toxicity of other antineoplastic agents. Concomitant treatment with other substances reported to be cardiotoxic or with cardiologically active substances (e.g. calcium antagonists) may increase the risk for cardiotoxicity. Concomitant therapy with other liposomal or lipid-complexed substances or intravenous fat emulsions could change the pharmacokinetic profile of Myocet.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use an effective contraceptive during treatment with Myocet and up to 6 months following discontinuation of therapy.

Pregnancy
Due to the known cytotoxic, mutagenic and embryotoxic properties of doxorubicin, Myocet should not be used during pregnancy unless clearly necessary.

Breast-feeding
Women receiving Myocet should not breastfeed.

4.7 Effect on ability to drive and use machines

Myocet has been reported to cause dizziness. Patients who suffer from this should avoid driving and operating machinery.

4.8 Undesirable effects

During clinical trials, the most frequently reported adverse reactions were nausea/vomiting (73%), leucopoenia (70%), alopecia (66%), neutropenia (46%), asthenia/fatigue (46%), stomatitis/mucositis (42%), thrombocytopenia (31%) and anaemia (30%).

The following adverse reactions have been reported with Myocet during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, not known (cannot be estimated from the available data).

	All grades	**Grades ≥ 3**
Infections and infestations		
Neutropenic fever	Very common	Very common
Infections	Very common	Common
Herpes zoster	Uncommon	Uncommon
Sepsis	Uncommon	Uncommon
Injection site infection	Uncommon	Not known
Blood and lymphatic system disorders		
Neutropenia	Very common	Very common
Thrombocytopenia	Very common	Very common
Anaemia	Very common	Very common
Leucopenia	Very common	Very common
Lymphopenia	Common	Common
Pancytopenia	Common	Uncommon
Neutropenic sepsis	Uncommon	Uncommon
Purpura	Uncommon	Uncommon
Metabolism and nutrition disorders		
Anorexia	Very common	Very common
Dehydration	Common	Very common
Hypokalaemia	Common	Uncommon
Hyperglycaemia	Uncommon	Uncommon
Psychiatric disorders		

	All grades	Grades ≥ 3
Agitation	Uncommon	Not known
Nervous system disorders		
Insomnia	Common	Uncommon
Abnormal gait	Uncommon	Uncommon
Dysphonia	Uncommon	Not known
Somnolence	Uncommon	Not known
Cardiac disorders		
Arrhythmia	Common	Uncommon
Cardiomyopathy	Common	Common
Congestive cardiac failure	Common	Common
Pericardial effusion	Uncommon	Uncommon
Vascular disorders		
Hot flushes	Common	Uncommon
Hypotension	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Chest pain	Common	Uncommon
Dyspnoea	Common	Uncommon
Epistaxis	Common	Uncommon
Haemoptysis	Uncommon	Not known
Pharyngitis	Uncommon	Not known
Pleural effusion	Uncommon	Uncommon
Pneumonitis	Uncommon	Uncommon
Gastrointestinal disorders		
Nausea/vomiting	Very common	Very common
Stomatitis/mucositis	Very common	Common
Diarrhoea	Very common	Common
Constipation	Common	Uncommon
Oesophagitis	Common	Uncommon
Gastric ulcer	Uncommon	Uncommon
Hepato-biliary disorders		
Increased hepatic transaminases	Common	Uncommon
Increased alkaline phosphatase	Uncommon	Uncommon
Jaundice	Uncommon	Uncommon
Increased serum bilirubin	Uncommon	Not known
Skin and subcutaneous tissue disorders		
Alopecia	Very Common	Common
Rash	Common	Not known
Palmar-plantar erythrodysaesthesia syndrome	Not known	Not known
Nail disorder	Common	Uncommon
Pruritus	Uncommon	Uncommon
Folliculitis	Uncommon	Uncommon
Dry skin	Uncommon	Not known
Musculoskeletal, connective tissue and bone disorders		
Back pain	Common	Uncommon

	All grades	Grades ≥ 3
Myalgia	Common	Uncommon
Muscle weakness	Uncommon	Uncommon
Renal and urinary disorders		
Haemorrhagic cystitis	Uncommon	Uncommon
Oliguria	Uncommon	Uncommon
General disorders and administration site conditions		
Asthenia/Fatigue	Very Common	Common
Fever	Very common	Common
Pain	Very Common	Common
Rigors	Very Common	Uncommon
Dizziness	Common	Uncommon
Headache	Common	Uncommon
Weight loss	Common	Uncommon
Injection site reaction	Uncommon	Uncommon
Malaise	Uncommon	Not known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Acute overdose with Myocet will worsen toxic side effects. Treatment of acute overdose should focus on supportive care for expected toxicity and may include hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group*:* Antineoplastic agents, anthracyclines and related substances, ATC code: L01DB01

The active substance in Myocet is doxorubicin HCl. Doxorubicin may exert its antitumour and toxic effects by a number of mechanisms including inhibition of topoisomerase II, intercalation with DNA and RNA polymerases, free radical formation and membrane binding. Liposomal-encapsulated compared with conventional doxorubicin was not found more active in doxorubicin resistant cell lines *in vitro.* In animals, liposome-encapsulated doxorubicin reduced the distribution to heart and gastrointestinal mucosa compared with conventional doxorubicin, while antitumoural efficacy in experimental tumours was maintained.

Myocet (60 mg/m^2) + CPA (600 mg/m^2) was compared with conventional doxorubicin + CPA (at the same doses) and Myocet (75 mg/m^2) + CPA (600 mg/m^2) was compared to epirubicin + CPA (at the same doses). In a third trial, Myocet (75 mg/m^2) monotherapy was compared with conventional doxorubicin monotherapy (at the same dose). Findings regarding response rate and progression-free survival are provided in Table 3.

Table 3
Antitumour efficacy summary for combination and single-agent studies

	Myocet/CPA (60/600 mg/m^2) (n=142)	Dox 60/CPA (60/600 mg/m^2) (n=155)	Myocet/CPA (75/600 mg/m^2) (n=80)	Epi/CPA (75/600 mg/m^2) (n=80)	Myocet (75 mg/m^2) (n=108)	Dox (75 mg/m^2) (n=116)
Tumour response rate	43%	43%	46%	39%	26%	26%
Relative Risk (95% C.I.)	1.01 (0.78-1.31)		1.19 (0.83-1.72)		1.00 (0.64-1.56)	
Median PFS (months)[a]	5.1	5.5	7.7	5.6	2.9	3.2
Risk Ratio (95% C.I.)	1.03 (0.80-1.34)		1.52 (1.06-2.20)		0.87 (0.66-1.16)	

Abbreviations: PFS, progression-free survival; Dox, doxorubicin; Epi, epirubicin; Relative Risk, comparator taken as reference; Risk Ratio, Myocet taken as reference
[a] Secondary endpoint

5.2 Pharmacokinetic properties

The plasma pharmacokinetics for total doxorubicin in patients receiving Myocet shows a high degree of inter-patient variability. In general however, the plasma levels of total doxorubicin are substantially higher with Myocet than with conventional doxorubicin, while the data indicate that peak plasma levels of free (not liposome-encapsulated) doxorubicin are lower with Myocet than with conventional doxorubicin. Available pharmacokinetic data preclude conclusions regarding the relationship between plasma levels of total/free doxorubicin and its influence on the efficacy/safety of Myocet. The clearance of total doxorubicin was 5.1 ± 4.8 l/h and the volume of distribution at steady state (V_d) was 56.6 ± 61.5 l whereas after conventional doxorubicin, clearance and V_d were 46.7 ± 9.6 l/h and 1,451 ± 258 l, respectively. The major circulating metabolite of doxorubicin, doxorubicinol, is formed via aldo-keto-reductase. The peak levels of doxorubicinol occur in the plasma later with Myocet than with conventional doxorubicin.

The pharmacokinetics of Myocet have not been specifically studied in patients with renal insufficiency. Doxorubicin is known to be eliminated in large part by the liver. A dose reduction of Myocet has been shown to be appropriate in patients with impaired hepatic function (see section 4.2 for dosage recommendations).

Substances that inhibit P-glycoprotein (P-Gp) have been shown to alter the disposition of doxorubicin and doxorubicinol (see also section 4.5).

5.3 Preclinical safety data

Studies of genotoxicity, carcinogenicity and reproductive toxicity of Myocet have not been performed but doxorubicin is known to be both mutagenic and carcinogenic and may cause toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Myocet doxorubicin HCl
- lactose

Myocet liposomes
- phosphatidylcholine

- cholesterol
- citric acid
- sodium hydroxide
- water for injections

Myocet buffer
- sodium carbonate
- water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months

Chemical and physical in-use stability after reconstitution has been demonstrated for up to 8 hours at 25°C, and for up to 5 days at 2°C – 8°C.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Myocet is available in cartons containing 1 set or 2 sets of the three constituents. Not all pack-sizes may be marketed.

Myocet doxorubicin HCl
Type I glass vials sealed with grey butyl rubber stoppers and orange flip-off aluminium seals, containing 50 mg of doxorubicin HCl lyophilised powder.

Myocet liposomes
Type I flint glass tubing vials sealed with siliconised grey stopper and green flip-off aluminium seals, containing not less than 1.9 ml of liposomes.

Myocet buffer
Glass vials sealed with siliconised grey stopper and blue aluminium flip-off seals, containing not less than 3 ml of buffer.

6.6 Special precautions for disposal and other handling

Preparation of Myocet
Aseptic technique must be strictly observed throughout handling of Myocet since no preservative is present.

Caution should be exercised in the handling and preparation of Myocet. The use of gloves is required

Step 1. Set up
Two alternative heating methods can be used : a Techne DB-3 Dri Block heater or a water bath:

- Turn on the Techne DB-3 Dri Block heater and set the controller to 75°C-76°C. Verify the temperature set point by checking the thermometer(s) on each heat block insert.
- If using a water bath, turn on the water bath and allow it to equilibrate at 58°C (55°C-60°C). Verify the temperature set point by checking the thermometer.

(Please note that whilst the control settings on the water bath and heat block are set to different levels the temperature of the vial contents are in the same range (55°C-60°C)).

Remove the carton of Myocet constituents from the refrigerator.

Step 2. Reconstitute doxorubicin HCl

- Withdraw 20 ml sodium chloride solution for injection (0.9%), (not provided in the package), and inject into each Myocet doxorubicin HCl, intended for preparation.
- Shake well in the inverted position to ensure doxorubicin is fully dissolved.

Step 3. Heat in water bath or dry heat block

- Heat the reconstituted Myocet doxorubicin HCl vial in the Techne DB-3 Dri Block heater with the thermometer in the block reading (75°C-76°C) for 10 minutes (not to exceed 15 minutes). If using the water bath heat the Myocet doxorubicin HCl vial with the thermometer temperature reading 55°C-60°C for 10 minutes (not to exceed 15 minutes).
- While heating proceed to step 4

Step 4. Adjust Ph of liposomes

- Withdraw 1.9 ml of Myocet liposomes. Inject into Myocet buffer vial to adjust the Ph of liposomes. Pressure build-up may require venting.
- Shake well.

Step 5. Add Ph-adjusted liposomes to doxorubicin

- Using syringe, withdraw the entire vial contents of Ph-adjusted liposomes from the Myocet buffer vial.
- Remove the reconstituted Myocet doxorubicin HCl vial from the water bath or dry heat block. SHAKE VIGOROUSLY. Carefully insert a pressure-venting device equipped with a hydrophobic filter. Then IMMEDIATELY (within 2 minutes) inject Ph-adjusted liposomes into vial of heated reconstituted Myocet doxorubicin HCl. Remove venting device.
- SHAKE VIGOROUSLY.
- WAIT for a minimum of 10 MINUTES before using, keeping the medicine at room temperature.

- The Techne DB-3 Dri Block Heater is fully validated for use in the constitution of Myocet. Three inserts, each with two 43.7mm openings per insert must be used. To ensure correct temperature control the use of a 35mm immersion thermometer is recommended.

The resulting reconstituted preparation of Myocet contains 50 mg of doxorubicin HCl/25 ml of liposomal dispersion (2 mg/ml).

After reconstitution the finished product must be further diluted in 0.9% (w/v) sodium chloride for injection, or 5% (w/v) glucose solution for injection to a final volume of 40 ml to 120 ml so that a final concentration of 0.4 mg/ml to 1.2 mg/ml doxorubicin is obtained.
Once constituted, the liposomal dispersion for infusion containing liposome-encapsulated doxorubicin should be a red orange opaque homogeneous dispersion. All parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration. Do not use the preparation if foreign particulate matter is present.

<u>Procedure for proper disposal</u>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/141/001-002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2000
Date of latest renewal: 02 July 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

GP-Pharm
Polígon Industrial Els Vinyets - Els Fogars,
Sector 2, Carretera Comarcal C244, km 22
08777 Sant Quintí de Mediona (Barcelona)
Spain

Teva Operations Poland Sp. z o.o.
ul. Mogilska 80
31-546 Kraków
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUHTORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (2 sets of 3 constituents)

1. NAME OF THE MEDICINAL PRODUCT

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion
Liposomal doxorubicin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Liposome–encapsulated doxorubicin corresponding to 50 mg doxorubicin hydrochloride

3. LIST OF EXCIPIENTS

Excipients:
Myocet doxorubicin HCl
lactose

Myocet liposomes
phosphatidylcholine, cholesterol, citric acid, sodium hydroxide, water for injections

Myocet buffer
sodium carbonate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, dispersion and solvent for concentrate for dispersion for infusion

Carton contents:
2 sets each containing:
1 vial Myocet doxorubicin HCl
1 vial Myocet liposomes
1 vial Myocet buffer

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Cytotoxic. Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/141/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING
(used with outer carton of 2 sets of 3 constituents)

1. NAME OF THE MEDICINAL PRODUCT

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion
Liposomal doxorubicin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Liposome–encapsulated doxorubicin corresponding to 50 mg doxorubicin hydrochloride

3. LIST OF EXCIPIENTS

Excipients:
Myocet doxorubicin HCl
lactose

Myocet liposomes
phosphatidylcholine, cholesterol, citric acid, sodium hydroxide, water for injections

Myocet buffer
sodium carbonate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, dispersion and solvent for concentrate for dispersion for infusion

Carton contents:
1 vial Myocet doxorubicin HCl
1 vial Myocet liposomes
1 vial Myocet buffer

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Cytotoxic. Any unused product or waste materials should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/141/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (1 set of 3 constituents)

1. NAME OF THE MEDICINAL PRODUCT

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion
Liposomal doxorubicin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Liposome–encapsulated doxorubicin corresponding to 50 mg doxorubicin hydrochloride

3. LIST OF EXCIPIENTS

Excipients:
Myocet doxorubicin HCl
lactose

Myocet liposomes
phosphatidylcholine, cholesterol, citric acid, sodium hydroxide, water for injections

Myocet buffer
sodium carbonate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, dispersion and solvent for concentrate for dispersion for infusion

Carton contents:
1 vial Myocet doxorubicin HCl
1 vial Myocet liposomes
1 vial Myocet buffer

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Cytotoxic. Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/141/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MYOCET DOXORUBICIN HCL VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Myocet
doxorubicin HCl
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

STICKER/TEAR OFF SECTION OF LABEL FOR RELABELLING THE MYOCET DOXORUBICIN HCL VIAL CONTAINING RECONSTITUTED FINISHED CONCENTRATE FOR DISPERSION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Myocet 50 mg concentrate for dispersion for infusion
Liposomal doxorubicin HCl
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Preparation Date: _____
Preparation Time: _____
Prepared By: _____

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MYOCET LIPOSOMES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Myocet liposomes

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.9 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MYOCET BUFFER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Myocet buffer

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion
Liposomal doxorubicin hydrochloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Myocet is and what it is used for

Myocet contains a medicine called “doxorubicin”, which damages tumour cells. This type of medicine is called “chemo-therapy”. The medicine is contained inside very small droplets of fat called “liposomes”.

Myocet is used in adult women for the first-line treatment of breast cancer that has spread (“metastatic breast cancer”). It is used with another medicine called “cyclophosphamide”. Please also read the patient information leaflet carefully that comes with that medicine.

2. What you need to know before you are given Myocet

Do not have Myocet:
- if you are allergic to doxorubicin or any of the other ingredients of this medicine (listed in section 6).

Do not have Myocet if this applies to you. If you are not sure, talk to your doctor or nurse before having Myocet.

Warning and precautions
Talk to your doctor or nurse before having Myocet.

Check with your doctor or nurse before having your medicine if:
- you have ever had heart problems such as a heart attack, heart failure or you have had high blood pressure for a long time
- you have liver problems.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before having Myocet.

Tests
Your doctor will do tests during your treatment to check that the medicine is working properly. They will also look out for any side effects such as blood problems or heart problems.

Radiation therapy

If you have already had radiation therapy, this may react with Myocet. You may get painful, red or dry skin. This can happen straight away or later on in your treatment.

Other medicines and Myocet
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Myocet can affect the way some other medicines work. Also some other medicines can affect the way Myocet works.

In particular tell your doctor or nurse if you are taking any of the following medicines:
- phenobarbital or phenytoin – for epilepsy
- warfarin – for thinning the blood
- streptozotocin – for cancer of the pancreas
- cyclosporine – for changing your immune system.

If any of the above apply to you (or you are not sure), please talk to your doctor or nurse before having Myocet.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before having Myocet.
- Myocet should not be used during pregnancy unless clearly necessary.
- Women having Myocet should not breast-feed.
- Women who could get pregnant should use effective contraception during treatment with Myocet and for 6 months after treatment.

Driving and using machines
You may feel dizzy after having Myocet. If you feel dizzy or are not sure how you feel, do not drive or use any tools or machines.

Myocet contains sodium
Myocet is available in cartons containing 1 set or 2 sets of 3 vials (not all pack-sizes may be marketed). When the 3 vials have been mixed together, your medicine contains about 108 mg sodium. This should be taken into consideration by patients on a controlled sodium diet.

3. How Myocet is given

This medicine is normally given by a doctor or nurse. It is given as a drip (infusion) into a vein.

How much you will be given
Your doctor will work out exactly how much you need. This is based on the size of your body (measured in “square metres” or “m^2”).

The recommended dose is between 60 and 75 mg of the medicine for each square meter of your body:
- this is given once every 3 weeks
- the medicine “cyclophosphamide” is given on the same day.

The doctor may give you a lower dose if they think you need it.

The number of times you have the drip depends on:
- the stage of your breast cancer
- how well your body responds to the medicine.

Treatment usually lasts for about 3 to 6 months.

If you get Myocet on your skin

Tell your doctor or nurse straight away if any medicine leaks from the drip (infusion) onto your skin. This is because Myocet can damage your skin. The drip will be stopped straight away. Ice will be put on the affected area for 30 minutes. Then the drip will be started in another vein.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Tell your doctor or nurse straight away if you notice any of the following side effects. These are signs of an allergic reaction and your drip (infusion) may have to be stopped:
- feeling breathless or a tight chest or throat
- headache or back pain
- fever or chills
- swollen or flushed face
- feeling tired, dizzy or light-headed.

If you notice any of the side effects listed above, tell your doctor or nurse straight away.

Other side effects

Very common (may affect more than 1 in 10 people)
- hair loss
- fever, chills, pain
- loss of appetite, diarrhoea, feeling or being sick (nausea or vomiting)
- reduced levels of certain blood cells – your doctor will regularly check your blood for this and decide if any treatment is required. Signs may include:
  - increased bruising
  - sore mouth, throat or mouth ulcers
  - reduced resistance to infection or fever
  - feeling tired or dizzy, having a lack of energy.

Common (may affect up to 1 in 10 people):
- muscle aches, back pain, headache
- difficulty breathing, chest pains
- feeling thirsty, pain or swelling of your food pipe
- shortness of breath, swollen ankles, muscle cramps. These may be signs of heart failure, uneven heart beat or a low potassium level in your blood
- liver function tests abnormal
- difficulty sleeping
- nose bleeds, hot flushes
- constipation, weight loss
- skin rash and nail problems.

Uncommon (may affect up to 1 in 100 people):
- coughing up blood
- feeling agitated, feeling sleepy
- low blood pressure, feeling unwell
- a change in how you walk, speech problems
- stomach pains which may be a sign of a stomach ulcer forming
- muscle weakness
- itchy, dry skin or swollen areas around hair roots
- swollen, red and blistering skin around where the drip was given

- high blood glucose level (your doctor will see this in a blood test)
- yellow skin or eyes. These may be signs of a liver problem called jaundice.
- change in how often you pass water (urine), pain on passing water or blood in your urine

Not Known: frequency cannot be estimated from the available data:
Redness and pain on the hands and feet

Myocet may cause some side effects that are related to how fast the drip is given. These include flushing, fever, chills, headaches and back pain. These side effects may stop if the drip is given more slowly over a longer period of time.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Myocet

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date stated on the label and carton.
- Store in a refrigerator (2ºC to 8ºC).
- From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at $2^{o}C – 8^{o}C$, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.
- Do not use this medicine if you notice that it shows evidence of discoloration, precipitation or any other particulate matter.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Myocet contains
- The active substance is liposome–encapsulated doxorubicin. This corresponds to 50 mg doxorubicin hydrochloride.
- The other ingredients are lactose (in the doxorubicin HCl vial), phosphatidylcholine, cholesterol, citric acid, sodium hydroxide and water for injections (in the liposomes vial), and sodium carbonate and water for injections (in the buffer vial).

What Myocet looks like and contents of the pack
Myocet consists of a powder, dispersion and solvent for concentrate for dispersion for infusion. It is supplied as a three-vial system: Myocet doxorubicin HCl, Myocet liposomes and Myocet buffer.

Once the content of the vials has been mixed together the resulting liposomal dispersion is orange-red and opaque.

Myocet is available in cartons containing 1 set or 2 sets of the three constituents. Not all pack-sizes may be marketed.

Marketing Authorisation Holder
Teva B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

Manufacturer
GP-Pharm
Polígon Industrial Els Vinyets - Els Fogars,
Sector 2, Carretera Comarcal C244, km 22
08777 Sant Quintí de Mediona (Barcelona)
Spain

Teva Operations Poland Sp. z o.o.
ul. Mogilska 80
31-546 Kraków
Poland

This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

PREPARATION GUIDE

Myocet 50 mg powder, dispersion and solvent for concentrate for dispersion for infusion
Liposomal doxorubicin hydrochloride

It is important you read the entire contents of this guide prior to the preparation of this medicinal product.

1. PRESENTATION

Myocet is supplied as a three-vial system: (1) Myocet doxorubicin HCl, (2) Myocet liposomes, and (3) Myocet buffer. In addition to these three components, 0.9% (w/v) sodium chloride solution for injection will also be required for the reconstitution of the doxorubicin HCl. Myocet must be reconstituted prior to administration.

2. RECOMMENDATIONS FOR SAFE HANDLING

The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted, namely:

- Personnel should be trained to reconstitute the medicinal product.
- Pregnant staff should be excluded from handling the medicinal product.
- Personnel handling this medicinal product during reconstitution should wear protective clothing including masks, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in a high-risk, waste disposal bag for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

3. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

Aseptic technique must be strictly observed throughout handling of Myocet since no preservative is present.

3.1 Preparation of Myocet

Step 1. Set up
Two alternative heating methods can be used : a Techne DB-3 Dri Block heater or a water bath:

- Turn on the Techne DB-3 Dri Block heater and set the controller to 75°C-76°C. Verify the temperature set point by checking the thermometer(s) on each heat block insert.
- If using a water bath, turn on the water bath and allow it to equilibrate at 58°C (55°C-60°C). Verify the temperature set point by checking the thermometer.

(Please note that whilst the control settings on the water bath and heat block are set to different levels the temperature of the vial contents are in the same range (55°C-60°C)).

- Remove the carton of Myocet constituents from the refrigerator.

Step 2. Reconstitute doxorubicin HCl

- Withdraw 20 ml sodium chloride solution for injection (0.9%), (not provided in the package), and inject into each Myocet doxorubicin HCl, intended for preparation.
- Shake well in the inverted position to ensure doxorubicin is fully dissolved.

Step 3. Heat in water bath or dry heat block

- Heat the reconstituted Myocet doxorubicin HCl vial in the Techne DB-3 Dri Block heater with the thermometer in the block reading (75°C-76°C) for 10 minutes (not to exceed 15 minutes).
- If using the water bath heat the Myocet doxorubicin HCl vial with the thermometer temperature reading 55°C-60°C for 10 minutes (not to exceed 15 minutes).
- While heating proceed to step 4.

Step 4. Adjust pH of liposomes

- Withdraw 1.9 ml of Myocet liposomes. Inject into Myocet buffer vial to adjust the pH of liposomes. Pressure build-up may require venting.
- Shake well.

Step 5. Add pH-adjusted liposomes to doxorubicin

- Using a syringe, withdraw the entire vial contents of pH-adjusted liposomes from the Myocet buffer vial.
- Remove the reconstituted Myocet doxorubicin HCl vial from the water bath or dry heat block. SHAKE VIGOROUSLY. Carefully insert a pressure-venting device equipped with a hydrophobic filter. Then IMMEDIATELY (within 2 minutes) inject the pH-adjusted liposomes into the vial of heated reconstituted Myocet doxorubicin HCl. Remove venting device.
- SHAKE VIGOROUSLY.
- WAIT FOR A MINIMUM OF 10 MINUTES BEFORE USING, KEEPING THE MEDICINE AT ROOM TEMPERATURE.

The Techne DB-3 Dri Block Heater is fully validated for use in the constitution of Myocet. Three inserts, each with two 43.7mm openings per insert must be used. To ensure correct temperature control the use of a 35mm immersion thermometer is recommended.

The resulting reconstituted preparation of Myocet contains 50 mg of doxorubicin HCl/25 ml of concentrate for liposomal dispersion for infusion (2 mg/ml).

After reconstitution the finished product must be further diluted in 0.9% (w/v) sodium chloride solution for injection, or 5% (w/v) glucose solution for injection to a final volume of 40 ml to 120 ml

per 50 mg reconstituted Myocet so that a final concentration of 0.4 mg/ml to 1.2 mg/ml doxorubicin is obtained.

Once constituted, the liposomal dispersion for infusion containing liposome encapsulated doxorubicin should be a red-orange opaque homogeneous dispersion. All parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the preparation if foreign particulate matter is present.

It has been demonstrated that once reconstituted Myocet has a chemical and physical in-use stability at room temperature for up to 8 hours or in a refrigerator (2^{o}C-8^{o}C) for up to 5 days.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2^{o}C-8^{o}C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

Myocet should be administered by intravenous infusion over a period of 1 hour.
Warning: Myocet must not be administered by the intramuscular or subcutaneous route or as a bolus injection.

4. DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.