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 hepaticimpairment
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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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

27/01/2015

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