DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Alan R. Bergstrom
Sr. Manager, Regulatory Support
US Drug Regulatory Affairs & Compliance
Aventis Pharmaceuticals
SC3-735A
300 Somerset Corporate Blvd.
Parsippany, NJ 08807-2854

RE: NDA # 20-449
Taxotere® (docetaxel) for Injection
MACMIS ID# 10198

Dear Mr. Bergstrom:

This letter notifies Aventis Pharmaceuticals (Aventis) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, Aventis promoted Taxotere for the unapproved use of first–line treatment of locally advanced or metastatic breast cancer at their commercial exhibit booth at the 37th American Society of Clinical Oncology (ASCO) Annual Meeting held in San Francisco, California in May 2001. Our specific objections follow:

Promotion of an Unapproved Use

In the commercial exhibit booth, Aventis disseminated a promotional brochure[1] describing the safety or effectiveness of their drug Taxotere for the unapproved use of first–line treatment of locally advanced or metastatic breast cancer. This brochure was freely available to all attendees at the ASCO Annual Meeting and contained conclusionary statements such as:

> "Introducing A[driamycin]T[axotere]–the *only* taxane combination approved for the first–line treatment of locally advanced or metastatic breast cancer."
>
> "The emerging standard for first–line treatment of locally advanced or metastatic breast cancer."
>
> "AT– Manageable side effects, which were comparable to AC[yclophosphamide] and did not compromise quality of life."

[1] A two page promotional brochure titled "From a strong foundation comes a better combination" (GM E 01005 0193)

Taxotere is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy and patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Aventis has not demonstrated that Taxotere is safe or effective for any other uses at this time.

Requested Action

Aventis should immediately cease the distribution of these and other similar promotional materials for Taxotere that contain the same or similar claims or presentations. Aventis should submit a written response to DDMAC on or before August 9, 2001, describing its intent and plans to comply with the above. In its letter to DDMAC, Aventis should include the date on which this and other similarly violative materials were discontinued.

Aventis should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 10198 in addition to the NDA number. DDMAC reminds Aventis that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

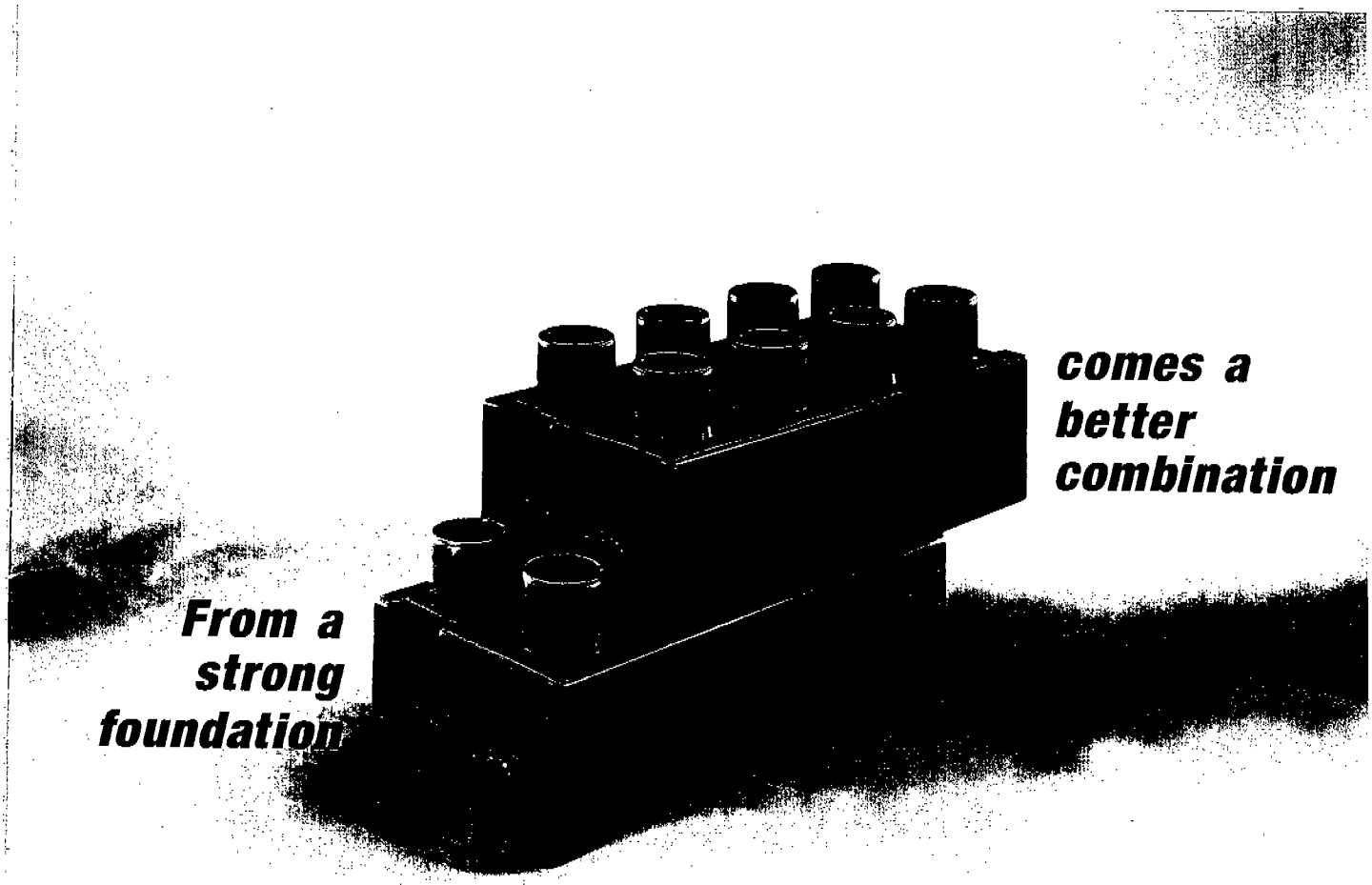
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
7/26/01 12:19:25 PM

Aventis

ONCOLOGY

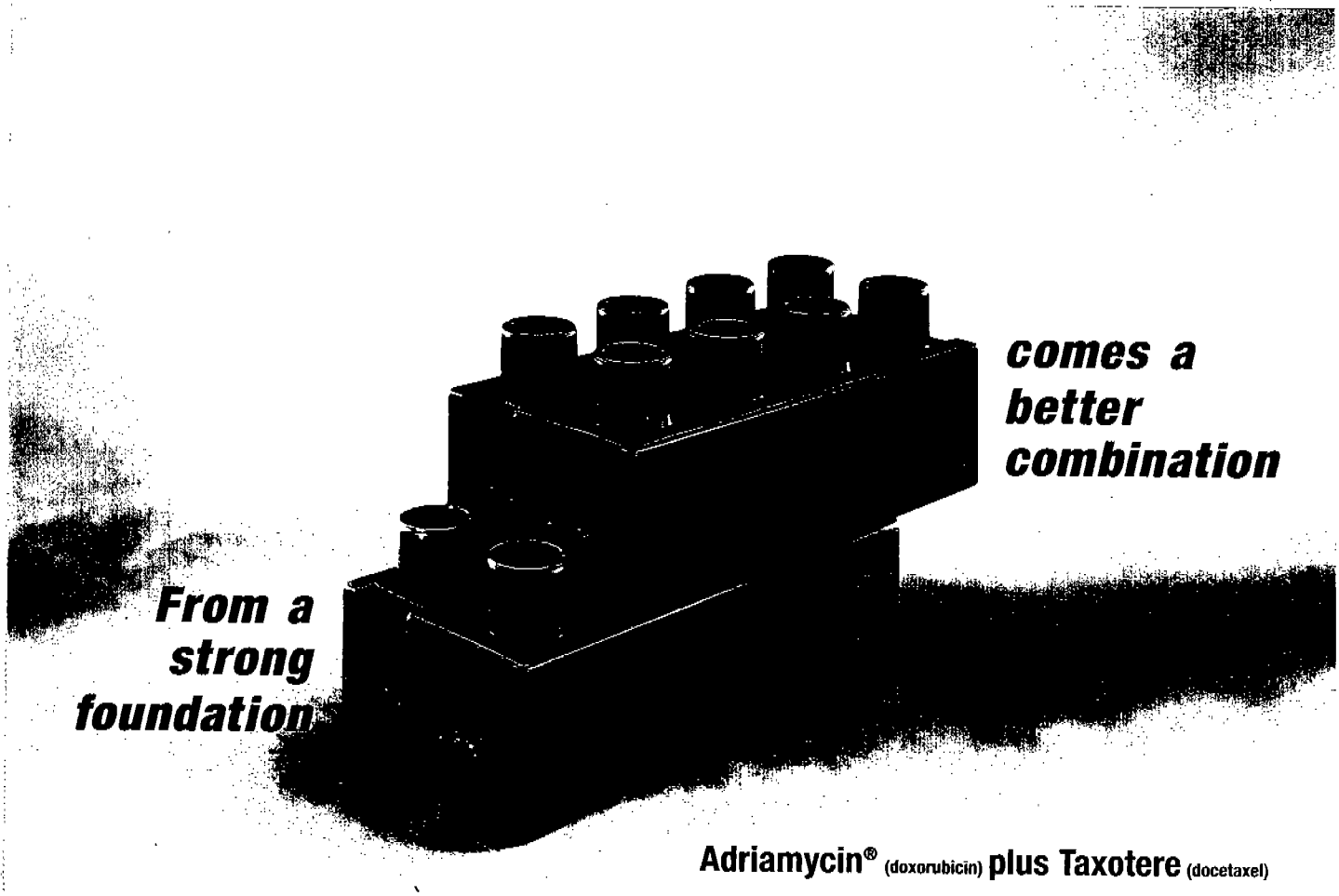


From a strong foundation

comes a better combination

Blocks provided by Taurus Toy Company.

TAXOTERE®
docetaxel



From a strong foundation

comes a better combination

Adriamycin® (doxorubicin) plus Taxotere (docetaxel)

The emerging standard for first-line treatment of locally advanced or metastatic breast cancer[1]

Blocks provided by Taurus Toy Company.

Aventis

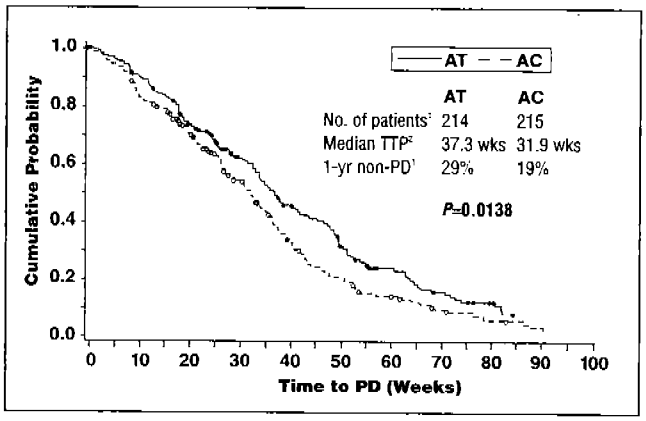
ONCOLOGY

Introducing AT—the *only* taxane combination approved for the first-line treatment of locally advanced or metastatic breast cancer[2]

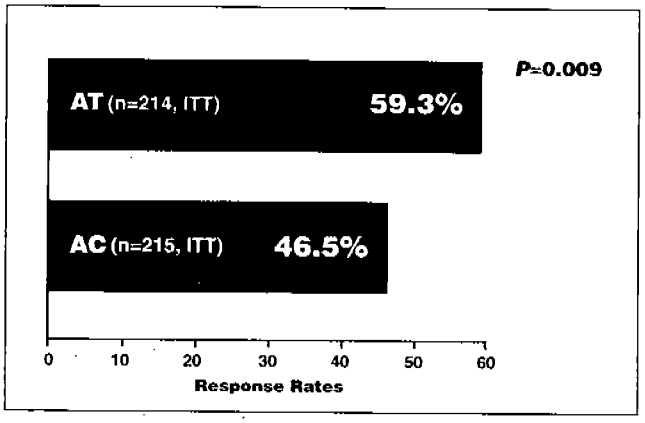
AT—Proven superiority over AC in a Phase III trial of metastatic breast cancer patients[2]

- Patients in the AT arm (n=214) received 50 mg/m² doxorubicin plus 75 mg/m² Taxotere and patients in the AC arm received 60 mg/m² doxorubicin plus 600 mg/m² cyclophosphamide; both regimens were administered every 3 weeks for a maximum of 8 cycles[1]

Significantly prolonged time to progression[1,2]



Significantly higher objective response rate[2]



- In the evaluable patient population (n=390), the objective response rate for AT was 64.9% vs 50.3% for AC, *P*=0.004[1]

- The complete response (CR) rate was also slightly higher in the AT arm vs the AC arm (ITT: 10.3% vs 7.4%; evaluable: 11.5% vs 8.0%, *P*=NS)[1]

AT—Manageable side effects, which were comparable to AC and did not compromise quality of life*[2]

- In this trial, the most common severe side effects were myelosuppression, asthenia, and gastrointestinal events, with <10% incidence of severe nonhaematologic side effects in both treatment arms; alopecia was nearly universal in both treatment arms[1]

- Recommended dosage: 75 mg/m² Taxotere plus 50 mg/m² doxorubicin administered day 1 every 3 weeks[2]

Taxotere should not be given to patients with abnormal liver function, low neutrophil count, or severe hypersensitivity to Taxotere or polysorbate 80.[2] Please see full prescribing information for complete details including dosage and steroid premedication regimen.

*Quality of life was comparable between the 2 treatment arms based on the QLQ-C30 and did not deteriorate during treatment and follow-up.[1]

Please see brief summary of full prescribing information on next page.
Full prescribing information available upon request.

TAXOTERE®
docetaxel

References:
1. Data on file, RP 56797-V-306, Aventis Pharma.
2. Taxotere® Prescribing Information, Aventis Pharma.

TAXOTERE®
docetaxel

ABBREVIATED PRESCRIBING INFORMATION for TAXOTERE® (docetaxel) 20 or 80 mg

TAXOTERE® (docetaxel) concentrate for solution for infusion is available in single-dose vials containing 20 or 80 mg in 0.5 or 2.0 ml of polysorbate 80, respectively with a solvent vial (13% ethanol in water for injections). **PHARMACOLOGICAL PROPERTIES:** Docetaxel promotes the assembly of tubulin into stable microtubules and inhibits their disassembly. **INDICATIONS:** Locally advanced or metastatic breast cancer in combination with doxorubicin in patients who have not previously received cytotoxic therapy. Locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent. Locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of prior chemotherapy. **DOSAGE:** 75 mg/m² in combination therapy with doxorubicin (50 mg/m²) for breast cancer. 100 mg/m² for breast cancer and 75 mg/m² for NSCLC, as a one-hour infusion every three weeks. All patients must be pretreated with an oral corticosteroid for 3 days starting one day before each TAXOTERE administration. **Dosage adjustments during treatment:** TAXOTERE should be administered when the neutrophil count is ≥ 1,500 cells/mm³. In patients with either febrile neutropenia, neutrophil < 500 cells/mm³ for > 7 days, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms, the dose should be reduced by 25%. If these reactions continue, the dosage should either be decreased to 60 mg or treatment discontinued. No data are available in patients with hepatic impairment treated by docetaxel in combination. **Dosage adjustments in patients with elevated liver function tests:** Patients with elevated ALT and/or AST > 1.5 times the upper limit of the normal range (ULN) concurrent with increases in alkaline phosphatase > 2.5 times the ULN, the recommended dose of TAXOTERE is 75 mg/m². In patients with serum bilirubin > ULN and/or ALT/AST values > 3.5 times the ULN associated with alkaline phosphatase > 6 times the ULN, TAXOTERE should not be used unless strictly indicated. **CONTRAINDICATIONS:** Hypersensitivity reactions to docetaxel or polysorbate 80; Baseline neutrophil count of < 1,500 cells/mm³; Severe liver impairment; Pregnancy or breast feeding. **WARNINGS AND PRECAUTIONS: Haematology:** Neutropenia is the most frequent adverse reaction and may require dosage reduction (see Dosage adjustments). Frequent monitoring of complete blood counts is required in all patients receiving docetaxel. **Severe hypersensitivity** reactions require immediate discontinuation and appropriate therapy and should not be rechallenged. Minor **hypersensitivity** reactions do not require interruption of therapy. **Cutaneous and CNS:** Localised skin erythema or severe neurosensory signs and/or symptoms may lead to dosage reduction, or treatment interruption or discontinuation. **Fluid retention:** Corticosteroid premedication can reduce the incidence and severity of fluid retention. Patients with pleural effusion, pericardial effusion and ascites should be monitored closely. **Liver function tests** (LFTs) should be measured at baseline and before each cycle. **Contraceptive** measures must be taken during and for > 3 months after therapy. **INTERACTIONS:** Caution when treating patients with drugs metabolized by cytochrome P450-3A. **SIDE EFFECTS** (In patients at 100 mg/m² single agent and 75 mg/m² in combination, respectively): **Haematology:** Severe neutropenia (76.4% and 91.7%); Fever with severe neutropenia (11.8% and 34.1%); Infectious episodes (20% with 5.7% severe, and 35.3% with 7.8% severe); Thrombocytopenia (7.8% and 28.1%); Anemia (90.4% with 8.9% severe and 96.1% with 9.4% severe). **Hypersensitivity** reactions (25.9% with 5.3% severe and 4.7% with 1.2% severe) resolved after discontinuing the infusion and appropriate therapy. Reversible **cutaneous** reactions (56.6% and 13.6%) with 73% of these events reversed within 21 days; Nail disorders (27.9% and 20.2%). **Fluid retention** (64.1% with 6.5% severe and 35.7% with 1.2% severe). The median cumulative dose to onset was 818.9 mg/m². The median cumulative dose to treatment discontinuation was more than 1.000 mg/m². **Gastrointestinal:** Nausea (40.5% and 64%); Vomiting (24.5% and 45%); Diarrhea (40.6% and 45.7%); Anorexia (16.8% and 8.5%); Constipation (9.8% and 14.3%); Stomatitis (41.8% and 58.1%); **Neuro-sensory** signs and/or symptoms (50% with 4.1% severe and 30.2% with 0.4% severe) and **neuro-motor** events (13.8% with 4% severe and 2.3% with 0.4% severe). The events were spontaneously reversible within 3 months in 35.3% Pts. **Cardiovascular:** Hypotension (3.8% and 0.4%); Dysrhythmia (4.1% and 1.2%). **Infusion site reactions** were generally mild and occurred in 5.6% and 3.1% Pts, respectively. **LFTs** Increases in AST, ALT, bilirubin and alkaline phosphatase > 2.5 times the ULN were observed in < 5% Pts treated at 100 mg/m². In patients treated in combination, less than 1% of patients experienced grade 3-4 increase in AST, ALT and grade 3-4 increase in bilirubin and alkaline phosphatase were observed in less than 2.5% of the patients. **Others:** Alopecia (79% and 94.6%); Severe asthenia (11.2% and 8.1%); Myalgias (20% and 8.5%); Pain (16.5% and 17.1%). **Continuing Surveillance:** Rare cases of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, neutropenic enterocolitis, venous thromboembolic events, myocardial infarction, pulmonary oedema in association with fluid retention, acute respiratory distress syndrome, interstitial pneumonia and radiation recall phenomenon. **CLINICAL:** Two randomized phase III comparative studies, involving respectively 326 alkylating and 392 anthracycline failure metastatic breast cancer Pts, have been performed with docetaxel at the dose of 100 mg/m² every 3 weeks. In anthracycline failure Pts, the response rate (RR) was 33% with TAXOTERE versus 12% with a combination of mitomycin and vinblastine. TAXOTERE prolonged the time to progression (TPP) (19 weeks versus 11 weeks) and the overall survival (11 months versus 9 months). In alkylating failure Pts, the RR was 52% with TAXOTERE versus 37% with doxorubicin. The TPP was prolonged (27 weeks with TAXOTERE versus 23 weeks with doxorubicin), and the time to response was shortened (12 weeks versus 23 weeks). One large randomized phase III study (429 previously untreated metastatic breast cancer Pts) has been performed with doxorubicin (50 mg/m²) in combination with docetaxel (75 mg/m²) versus doxorubicin (60 mg/m²) in combination with cyclophosphamide (600 mg/m²): median TPP (37.3 weeks versus 31.9 weeks), overall RR (59.3% versus 46.5%). In one phase III study, in previously treated NSCLC patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 75 mg/m² compared to Best Supportive Care (BSC). The 1-year survival rate was also significantly longer in docetaxel (40%) versus BSC (16%). There was less use of morphinic analgesic ($p<0.01$), non-morphinic analgesics ($p<0.01$), other disease-related medications ($p=0.06$) and radiotherapy ($p<0.01$) in patients treated with docetaxel at 75 mg/m² compared to those with BSC. The overall response rate was 6.8% in the evaluable patients, and the median duration of response was 26.1 weeks. **KINETICS** are dose-independent. Excretion is mainly faecal following hepatic metabolism. Docetaxel is > 95% protein bound. In a population pharmacokinetic analysis neither age nor sex had an impact on kinetics; there was a 27% decrease in total clearance in patients with elevated LFTs. **PRECLINICAL:** Docetaxel is mutagenic consistent with its pharmacological activity. **SHELF-LIFE:** Vials should be stored between +2°C and +25°C and protected from bright light. The shelf-life is respectively 18 and 24 months for TAXOTERE 20 and 80 mg. **INSTRUCTIONS FOR USE:** TAXOTERE must be diluted with the entire contents of the solvent vial: TAXOTERE premix solution (10 mg docetaxel/ml) unless used immediately to prepare the infusion solution, can be stored for up to 8 hours either between +2°C and +8°C or at room temperature. To prepare, inject the appropriate amount of TAXOTERE premix solution into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride solution or 5% glucose solution to produce a final concentration not exceeding 0.74 mg/ml. Use the infusion solution within the 4 hours. **MARKETING AUTHORISATION HOLDER:** Aventis Pharma S.A. 20 avenue Raymond Aron 92165 Antony Cedex France **AUTHORISATION NUMBERS:** EU/1/95/002/001 and EU/1/95/002/002 **DATE OF FIRST AUTHORISATION:** November 1995. **DATE OF REVISION:** August 2000.

See European Summary of Product Characteristics for further information.

GM E 01005 0193