ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT: Zerit® 15 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Capsules each containing 15 mg of stavudine.

3. PHARMACEUTICAL FORM: capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate.

Efficacy as measured by clinical endpoints has been shown in patients after prolonged prior zidovudine monotherapy.

4.2 Posology and method of administration

Adults and children over the age of 12 years: The recommended starting dosage is:

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Zerit® should be taken at least one hour prior to meals (see 5.2). The therapy should be initiated by a doctor experienced in the management of HIV infection.

Dose adjustments

Peripheral neuropathy is usually characterized by persistent numbness, tingling, or pain in the feet and/or hands. If these symptoms develop, Zerit® therapy should be interrupted. Stavudine-related peripheral neuropathy should resolve if therapy is withdrawn promptly although some patients may experience a temporary worsening of symptoms following discontinuation. If symptoms resolve satisfactorily, resumption of treatment with Zerit® at 50% of the previous dosage may be considered.

Clinically significant elevations of hepatic transaminase (ALT/AST, > 5 x upper limit of normal, ULN) should be managed in the same way as peripheral neuropathy.

Hepatic impairment: no initial dosage adjustment is necessary
Renal impairment: the following dosages are recommended:

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There are insufficient data to recommend a dosage adjustment for patients with a creatinine clearance < 10 mL/min, or for those patients undergoing dialysis.

4.3 Contra-indications

Zerit® is contraindicated in patients with hypersensitivity to stavudine or to any of the excipients (see 6.1).

4.4 Special warnings and special precautions for use

Patients with a history of peripheral neuropathy are at increased risk for development of neuropathy. If Zerit® must be administered in this setting, careful monitoring is essential.

Patients with a history of pancreatitis had an incidence of approximately 5% on Zerit®, as compared to approximately 2% in patients without such a history. Patients with a high risk of pancreatitis or those receiving products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

Clinically significant elevations of ALT and AST may require dose modifications (see 4.2)

Elderly: Zerit® has not been specifically investigated in patients over the age of 65.

Children under the age of 12 years: there is insufficient documentation on the use of Zerit® in children.

Lactose intolerance: the capsules contain lactose (120 mg). This quantity is probably not sufficient to induce specific symptoms of intolerance.

4.5 Interactions with other medicaments and other forms of interaction

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted drugs are possible.

There are no clinical data with respect to the interaction between stavudine and zidovudine (see 5.1).
4.6 Pregnancy and lactation

Embryo-foetal toxicities were seen only at high exposure levels in animals. Clinical experience in pregnant women is lacking. Until additional data become available, Zerit® should be given during pregnancy only after special consideration.

An *ex vivo* study using a term human placenta model demonstrated that stavudine reaches the foetal circulation by simple diffusion. A rat study also showed placental transfer of stavudine, with the foetal tissue concentration approximately 50% of the maternal plasma concentration.

The data available on stavudine excretion into human breast milk are insufficient to assess the risk to the child. Studies in lactating rats showed that stavudine is excreted in breast milk. Therefore, mothers should be instructed to discontinue breast feeding prior to receiving Zerit®. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

There is no indication that Zerit® affects this ability.

4.8 Undesirable effects

Many of the serious undesirable effects reported in clinical trials with Zerit® are consistent with the course of HIV-infection, or with the side effects of concomitant therapies. More *Pneumocystis carinii* pneumonia (PCP) cases were observed in patients on stavudine than in patients on zidovudine. A potential interaction, although unlikely, between PCP prophylaxis agents and stavudine therapy has not yet been studied.

The major clinical toxicity is dose-related peripheral neuropathy requiring dose modification (see 4.2). The yearly rate of neuropathy in an expanded access programme of approximately 12,000 patients with advanced HIV disease (median CD4: 44 cells/mm³) and prolonged prior treatment with other antiretroviral nucleosides was 24% and 19% for patients receiving 40 or 20 mg twice daily, respectively. The intensity of this complaint was usually mild and patients usually experienced resolution of symptoms after dose reduction or interruption. The 24-week rates of therapy discontinuation due to neuropathy in this population were 13% and 10% for the two doses, respectively.

In a comparative trial involving patients with less advanced HIV-infection (median CD4: 250 cells/mm³), after a median duration of 79 weeks on Zerit® treatment versus 53 weeks on zidovudine, asymptomatic elevations of AST and ALT (5 times ULN) were observed while receiving Zerit®. Yearly rates of peripheral neuropathy in this comparative trial were 12% for Zerit® and 4% for zidovudine.

Pancreatitis, occasionally fatal, has been reported in up to 2-3% of patients enrolled in the clinical studies. Other undesirable effects reported from > 5% of patients in the zidovudine-comparative trial which are considered potential adverse reactions included: headache, chills/fever, malaise, diarrhoea, constipation, dyspepsia, asthenia, anorexia, nausea/vomiting, pneumonia, pain, chest-, abdominal-, and back-pain, myalgia, arthralgia, insomnia, depression, anxiety, flu syndrome, sweating, dizziness, dyspnoea, allergic reaction, rash, maculopapular rash, pruritus, benign skin neoplasms, peripheral neurologic symptoms, neuropathy, lymphadenopathy, and neoplasms.

Abnormalities of laboratory tests in the same trial were infrequent. Clinically significant elevations of ALT and AST were reported in 13% and 11% of Zerit® recipients, respectively, and in 11% and 10% of zidovudine recipients, respectively. Alkaline phosphatase > 5 times ULN, and bilirubin > 2.5 times ULN each were reported in 1% of Zerit® recipients and in 0% and 3% of zidovudine recipients, respectively. Neutropenia (< 750 cells/mm³) was reported in 5% and 9%, thrombocytopenia (platelets < 50,000/mm³) in 3% of Zerit® and zidovudine
recipients, amylase (> 1.0 times ULN) in 23% and 22% of Zerit® and zidovudine recipients, respectively.

4.9 Overdose

Experience in adults treated with up to 24 times the recommended dosage revealed no acute toxicity. Complications of chronic overdosage could include peripheral neuropathy and hepatic dysfunction. It is not known whether stavudine is dialysable by peritoneal- or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code J05AX04.

Stavudine, a thymidine analog, is an antiviral agent with \textit{in vitro} activity against HIV in human cells. It is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination.

\textit{In vitro} studies have shown that doxorubicin may inhibit the intracellular activation of stavudine. This activation may be inhibited by zidovudine but not by other antiviral drugs used in HIV infection. Stavudine does not inhibit the activation of zidovudine; it is unknown whether stavudine affects the phosphorylation of other antiviral and cytotoxic drugs used in HIV infection.

HIV-1 strains with reduced sensitivity to stavudine have been isolated following \textit{in vitro} passage, and in some post-treatment patient isolates. However, few data are available addressing the development of HIV-resistance to stavudine \textit{in vivo}, or the development of cross-resistance to other nucleoside analogues.

5.2 Pharmacokinetic properties

\textbf{Adults:} The absolute bioavailability is 86 ± 18%. After multiple oral administration of 0.5 - 0.67 mg/kg doses, a Cmax value of 810 ± 175 ng/mL was obtained. Cmax and AUC increased proportionally with dose in the dose ranges, i.v. 0.0625 - 0.75 mg/kg, and oral 0.033 - 4.0 mg/kg.

A study in asymptomatic patients demonstrated that systemic exposure is similar while Cmax is lower and Tmax is longer, whether stavudine is administered under fasting conditions or after a standardized, high-fat meal. The clinical significance of this is unknown.

The apparent volume of distribution at steady state is 46 ± 15 L. Cerebrospinal fluid (CSF) levels of stavudine were not possible to detect until at least 2 hours after oral administration. Four hours after administration the CSF/plasma ratio was 0.39 ± 0.06. No significant accumulation of stavudine is observed with repeated administration every 6, 8, or 12 hours.

The terminal elimination half-life is 1.3 ± 0.2 hours after a single dose, and 1.4 ± 0.2 hours after multiple doses, and is independent of dose. \textit{In vitro}, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.

Total clearance of stavudine is 600 ± 90 mL/min, and renal clearance is 240 ± 50 mL/min, indicating active tubular secretion in addition to glomerular filtration. After i.v. administration, 42 ± 7% of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 34 ± 5% and 40 ± 12%, respectively. The remaining 60% of the drug is presumably eliminated by endogenous pathways.
The metabolism of stavudine has not been elucidated in humans. Studies in monkeys indicate that the majority of the dose that is not excreted unchanged in the urine (approximately 50%) is hydrolysed to thymine and sugar.

The pharmacokinetics of stavudine was independent of time, since the ratio between AUC(ss) at steady state and the AUC(0-t ) after the first dose was approximately 1. Intra- and interindividual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

Renal impairment: the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit® be adjusted in patients with reduced renal function (see 4.2).

Hepatic impairment: stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

5.3 Preclinical Safety Data

Animal data showed embryo-foetal toxicity at very high exposure levels. Stavudine was genotoxic in in vitro tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an in vivo test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues. Carcinogenicity studies are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171). The capsules are marked using edible printing ink.

6.2 Incompatibilities

None.

6.3 Shelf Life

24 months between 15°C and 30°C.

6.4 Special precautions for storage

Stored in tightly closed bottles at 15°C to 30°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant screw cap (60 capsules per bottle), or aclar/aluminum blisters with 14 capsules per card and 4 cards (56 capsules) per carton.

7. MARKETING AUTHORIZATION HOLDER:

Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom
8. **MARKETING AUTHORIZATION NUMBER(S):**

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:**

10. **DATE OF REVISION OF THE TEXT:**
1. **NAME OF THE MEDICINAL PRODUCT:** Zerit® 20 mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Capsules each containing 20 mg of stavudine.

3. **PHARMACEUTICAL FORM:** capsules

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**
Treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate.

Efficacy as measured by clinical endpoints has been shown in patients after prolonged prior zidovudine monotherapy.

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Zerit® should be taken at least one hour prior to meals (see 5.2). The therapy should be initiated by a doctor experienced in the management of HIV infection.

**Dose adjustments**

**Peripheral neuropathy** is usually characterized by persistent numbness, tingling, or pain in the feet and/or hands. If these symptoms develop, Zerit® therapy should be interrupted. Stavudine-related peripheral neuropathy should resolve if therapy is withdrawn promptly although some patients may experience a temporary worsening of symptoms following discontinuation. If symptoms resolve satisfactorily, resumption of treatment with Zerit® at 50% of the previous dosage may be considered.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiviral agent, ATC code J05AX04.

Stavudine, a thymidine analog, is an antiviral agent with in vitro activity against HIV in human cells. It is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination.

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Adults: The absolute bioavailability is 86 ± 18%. After multiple oral administration of 0.5 - 0.67 mg/kg doses, a Cmax value of 810 ± 175 ng/mL was obtained. Cmax and AUC increased proportionally with dose in the dose ranges, i.v. 0.0625 - 0.75 mg/kg, and oral 0.033 - 4.0 mg/kg.

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The terminal elimination half-life is 1.3 ± 0.2 hours after a single dose, and 1.4 ± 0.2 hours after multiple doses, and is independent of dose. In vitro, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.

Total clearance of stavudine is 600 ± 90 mL/min, and renal clearance is 240 ± 50 mL/min, indicating active tubular secretion in addition to glomerular filtration. After i.v. administration, 42 ± 7% of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 34 ± 5% and 40 ± 12%, respectively. The remaining 60% of the drug is presumably eliminated by endogenous pathways.
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**Renal impairment:** the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit® be adjusted in patients with reduced renal function (see 4.2).

**Hepatic impairment:** stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

5.3 **Preclinical Safety Data**

Animal data showed embryo-foetal toxicity at very high exposure levels. Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues. Carcinogenicity studies are ongoing.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171). The capsules are marked using edible printing ink.

6.2 **Incompatibilities**

None.

6.3 **Shelf Life**

24 months between 15°C and 30°C.

6.4 **Special precautions for storage**

Stored in tightly closed bottles at 15°C to 30°C.

6.5 **Nature and contents of container**

High-density polyethylene (HDPE) bottles with child resistant screw cap (60 capsules per bottle), or aclar/aluminum blisters with 14 capsules per card and 4 cards (56 capsules) per carton.

7. **MARKETING AUTHORIZATION HOLDER:**

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1. **NAME OF THE MEDICINAL PRODUCT:** Zerit® 30 mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Capsules each containing 30 mg of stavudine.

3. **PHARMACEUTICAL FORM:** capsules

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

Treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate.

Efficacy as measured by clinical endpoints has been shown in patients after prolonged prior zidovudine monotherapy.

4.2 **Posology and method of administration**

**Adults and children over the age of 12 years:** The recommended starting dosage is:

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**Dose adjustments**

**Peripheral neuropathy** is usually characterized by persistent numbness, tingling, or pain in the feet and/or hands. If these symptoms develop, Zerit® therapy should be interrupted. Stavudine-related peripheral neuropathy should resolve if therapy is withdrawn promptly although some patients may experience a temporary worsening of symptoms following discontinuation. If symptoms resolve satisfactorily, resumption of treatment with Zerit® at 50% of the previous dosage may be considered.

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Zerit® is contraindicated in patients with hypersensitivity to stavudine or to any of the excipients (see 6.1).

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Patients with a history of peripheral neuropathy are at increased risk for development of neuropathy. If Zerit® must be administered in this setting, careful monitoring is essential.

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Clinically significant elevations of ALT and AST may require dose modifications (see 4.2)

Elderly: Zerit® has not been specifically investigated in patients over the age of 65.

Children under the age of 12 years: there is insufficient documentation on the use of Zerit® in children.

Lactose intolerance: the capsules contain lactose (182 mg). This quantity is probably not sufficient to induce specific symptoms of intolerance.

4.5 Interactions with other medicaments and other forms of interaction

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted drugs are possible.

There are no clinical data with respect to the interaction between stavudine and zidovudine (see 5.1).
4.6 Pregnancy and lactation

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There is no indication that Zerit® affects this ability.

4.8 Undesirable effects

Many of the serious undesirable effects reported in clinical trials with Zerit® are consistent with the course of HIV-infection, or with the side effects of concomitant therapies. More Pneumocystis carinii pneumonia (PCP) cases were observed in patients on stavudine than in patients on zidovudine. A potential interaction, although unlikely, between PCP prophylaxis agents and stavudine therapy has not yet been studied.

The major clinical toxicity is dose-related peripheral neuropathy requiring dose modification (see 4.2). The yearly rate of neuropathy in an expanded access programme of approximately 12,000 patients with advanced HIV disease (median CD4: 44 cells/mm³) and prolonged prior treatment with other antiretroviral nucleosides was 24% and 19% for patients receiving 40 or 20 mg twice daily, respectively. The intensity of this complaint was usually mild and patients usually experienced resolution of symptoms after dose reduction or interruption. The 24-week rates of therapy discontinuation due to neuropathy in this population were 13% and 10% for the two doses, respectively.

In a comparative trial involving patients with less advanced HIV-infection (median CD4: 250 cells/mm³), after a median duration of 79 weeks on Zerit® treatment versus 53 weeks on zidovudine, asymptomatic elevations of AST and ALT (5 times ULN) were observed while receiving Zerit®. Yearly rates of peripheral neuropathy in this comparative trial were 12% for Zerit® and 4% for zidovudine.

Pancreatitis, occasionally fatal, has been reported in up to 2-3% of patients enrolled in the clinical studies. Other undesirable effects reported from > 5% of patients in the zidovudine-comparative trial which are considered potential adverse reactions included: headache, chills/fever, malaise, diarrhoea, constipation, dyspepsia, asthenia, anorexia, nausea/vomiting, pneumonia, pain, chest-, abdominal-, and back-pain, myalgia, arthralgia, insomnia, depression, anxiety, flu syndrome, sweating, dizziness, dyspnoea, allergic reaction, rash, maculopapular rash, pruritus, benign skin neoplasms, peripheral neurologic symptoms, neuropathy, lymphadenopathy, and neoplasms.

Abnormalities of laboratory tests in the same trial were infrequent. Clinically significant elevations of ALT and AST were reported in 13% and 11% of Zerit® recipients, respectively, and in 11% and 10% of zidovudine recipients, respectively. Alkaline phosphatase > 5 times ULN, and bilirubin > 2.5 times ULN each were reported in 1% of Zerit® recipients and in 0% and 3% of zidovudine recipients, respectively. Neutropenia (< 750 cells/mm³) was reported in 5% and 9%, thrombocytopenia (platelets < 50,000/mm³) in 3% of Zerit® and zidovudine...
recipients, amylase (> 1.0 times ULN) in 23% and 22% of Zerit® and zidovudine recipients, respectively.

4.9 Overdose

Experience in adults treated with up to 24 times the recommended dosage revealed no acute toxicity. Complications of chronic overdosage could include peripheral neuropathy and hepatic dysfunction. It is not known whether stavudine is dialysable by peritoneal- or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiviral agent, ATC code J05AX04.

Stavudine, a thymidine analog, is an antiviral agent with in vitro activity against HIV in human cells. It is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination.

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HIV-1 strains with reduced sensitivity to stavudine have been isolated following in vitro passage, and in some post-treatment patient isolates. However, few data are available addressing the development of HIV-resistance to stavudine in vivo, or the development of cross-resistance to other nucleoside analogues.

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**Adults:** The absolute bioavailability is 86 ± 18%. After multiple oral administration of 0.5 - 0.67 mg/kg doses, a Cmax value of 810 ± 175 ng/mL was obtained. Cmax and AUC increased proportionally with dose in the dose ranges, i.v. 0.0625 - 0.75 mg/kg, and oral 0.033 - 4.0 mg/kg.

A study in asymptomatic patients demonstrated that systemic exposure is similar while Cmax is lower and Tmax is longer, whether stavudine is administered under fasting conditions or after a standardized, high-fat meal. The clinical significance of this is unknown.

The apparent volume of distribution at steady state is 46 ± 15 L. Cerebrospinal fluid (CSF) levels of stavudine were not possible to detect until at least 2 hours after oral administration. Four hours after administration the CSF/plasma ratio was 0.39 ± 0.06. No significant accumulation of stavudine is observed with repeated administration every 6, 8, or 12 hours.

The terminal elimination half-life is 1.3 ± 0.2 hours after a single dose, and 1.4 ± 0.2 hours after multiple doses, and is independent of dose. In vitro, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.

Total clearance of stavudine is 600 ± 90 mL/min, and renal clearance is 240 ± 50 mL/min, indicating active tubular secretion in addition to glomerular filtration. After i.v. administration, 42 ± 7% of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 34 ± 5% and 40 ± 12%, respectively. The remaining 60% of the drug is presumably eliminated by endogenous pathways.
The metabolism of stavudine has not been elucidated in humans. Studies in monkeys indicate that the majority of the dose that is not excreted unchanged in the urine (approximately 50%) is hydrolysed to thymine and sugar.

The pharmacokinetics of stavudine was independent of time, since the ratio between AUC(ss) at steady state and the AUC(0-t) after the first dose was approximately 1. Intra- and interindividual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

**Renal impairment:** the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit® be adjusted in patients with reduced renal function (see 4.2).

**Hepatic impairment:** stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

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Animal data showed embryo-foetal toxicity at very high exposure levels. Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues. Carcinogenicity studies are ongoing.

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6.1 List of excipients

Lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171). The capsules are marked using edible printing ink.

6.2 Incompatibilities

None.

6.3 Shelf Life

24 months between 15°C and 30°C.

6.4 Special precautions for storage

Stored in tightly closed bottles at 15°C to 30°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant screw cap (60 capsules per bottle), or aclar/aluminum blisters with 14 capsules per card and 4 cards (56 capsules) per carton.

7. MARKETING AUTHORIZATION HOLDER:

Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom
8. MARKETING AUTHORIZATION NUMBER(S):

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:

10. DATE OF REVISION OF THE TEXT:
1. **NAME OF THE MEDICINAL PRODUCT:** Zerit® 40 mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Capsules each containing 40 mg of stavudine.

3. **PHARMACEUTICAL FORM:** capsules

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

Treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate.

Efficacy as measured by clinical endpoints has been shown in patients after prolonged prior zidovudine monotherapy.

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**Adults and children over the age of 12 years:** The recommended starting dosage is:

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Zerit® should be taken at least one hour prior to meals (see 5.2). The therapy should be initiated by a doctor experienced in the management of HIV infection.

**Dose adjustments**

**Peripheral neuropathy** is usually characterized by persistent numbness, tingling, or pain in the feet and/or hands. If these symptoms develop, Zerit® therapy should be interrupted. Stavudine-related peripheral neuropathy should resolve if therapy is withdrawn promptly although some patients may experience a temporary worsening of symptoms following discontinuation. If symptoms resolve satisfactorily, resumption of treatment with Zerit® at 50% of the previous dosage may be considered.

**Clinically significant elevations of hepatic transaminase** (ALT/AST, > 5 x upper limit of normal, ULN) should be managed in the same way as peripheral neuropathy.

**Hepatic impairment:** no initial dosage adjustment is necessary
Renal impairment: the following dosages are recommended:

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There are insufficient data to recommend a dosage adjustment for patients with a creatinine clearance < 10 mL/min, or for those patients undergoing dialysis.

4.3 Contra-indications

Zerit® is contraindicated in patients with hypersensitivity to stavudine or to any of the excipients (see 6.1).

4.4 Special warnings and special precautions for use

Patients with a history of peripheral neuropathy are at increased risk for development of neuropathy. If Zerit® must be administered in this setting, careful monitoring is essential.

Patients with a history of pancreatitis had an incidence of approximately 5% on Zerit®, as compared to approximately 2% in patients without such a history. Patients with a high risk of pancreatitis or those receiving products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

Clinically significant elevations of ALT and AST may require dose modifications (see 4.2)

Elderly: Zerit® has not been specifically investigated in patients over the age of 65.

Children under the age of 12 years: there is insufficient documentation on the use of Zerit® in children.

Lactose intolerance: the capsules contain lactose (238 mg). This quantity is probably not sufficient to induce specific symptoms of intolerance.

4.5 Interactions with other medicaments and other forms of interaction

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted drugs are possible.

There are no clinical data with respect to the interaction between stavudine and zidovudine (see 5.1).
4.6 Pregnancy and lactation

Embryo-foetal toxicities were seen only at high exposure levels in animals. Clinical experience in pregnant women is lacking. Until additional data become available, Zerit® should be given during pregnancy only after special consideration.

An ex vivo study using a term human placenta model demonstrated that stavudine reaches the foetal circulation by simple diffusion. A rat study also showed placental transfer of stavudine, with the foetal tissue concentration approximately 50% of the maternal plasma concentration.

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6.1 List of excipients

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6.2 Incompatibilities

None.

6.3 Shelf Life

24 months between 15°C and 30°C.

6.4 Special precautions for storage

Stored in tightly closed bottles at 15°C to 30°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant screw cap (60 capsules per bottle), or aclar/aluminum blisters with 14 capsules per card and 4 cards (56 capsules) per carton.

7. MARKETING AUTHORIZATION HOLDER:

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8. MARKETING AUTHORIZATION NUMBER(S):

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10. DATE OF REVISION OF THE TEXT:
1. **NAME OF THE MEDICINAL PRODUCT:** Zerit® Powder for oral solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Powder for oral solution containing 1 mg of stavudine per mL of constituted solution (200 mL per bottle).

3. **PHARMACEUTICAL FORM:** Powder for oral solution.

4. **CLINICAL PARTICULARS**

   4.1 **Therapeutic Indications**

   Treatment of HIV-infected patients in whom zidovudine is not or is no longer appropriate.

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   **Peripheral neuropathy** is usually characterized by persistent numbness, tingling, or pain in the feet and/or hands. If these symptoms develop, Zerit® therapy should be interrupted. Stavudine-related peripheral neuropathy should resolve if therapy is withdrawn promptly although some patients may experience a temporary worsening of symptoms following discontinuation. If symptoms resolve satisfactorily, resumption of treatment with Zerit® at 50% of the previous dosage may be considered.

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Clinically significant elevations of ALT and AST may require dose modifications (see 4.2)

Elderly: Zerit® has not been specifically investigated in patients over the age of 65.

Children under the age of 12 years: there is insufficient documentation on the use of Zerit® in children.

Diabetic patients: the constituted powder for oral solution contains 50 mg sucrose per mL of constituted solution.

4.5 Interactions with other medicaments and other forms of interaction

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The metabolism of stavudine has not been elucidated in humans. Studies in monkeys indicate that the majority of the dose that is not excreted unchanged in the urine (approximately 50%) is hydrolysed to thymine and sugar.
The pharmacokinetics of stavudine was independent of time, since the ratio between AUC(ss) at steady state and the AUC(0-t) after the first dose was approximately 1. Intra- and interindividual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

**Renal impairment:** the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit® be adjusted in patients with reduced renal function (see 4.2).

**Hepatic impairment:** stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

5.3 Preclinical Safety Data

Animal data showed embryo-foetal toxicity at very high exposure levels. Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues. Carcinogenicity studies are ongoing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cherry flavour, methylparaben, propylparaben, silicon dioxide, simethicone, sodium carboxymethylcellulose, sorbic acid, stearate emulsifiers and sucrose.

6.2 Incomptatibilities

None.

6.3 Shelf Life

24 months between 15°C and 30°C. After constitution, the solution may be stored for up to 30 days under refrigeration (2°C to 8°C) (see 6.4).

6.4 Special precautions for storage

Store and protect from excessive moisture in tightly closed bottles at 15°C to 30°C. After constitution, store the solution in tightly closed bottles under refrigeration (2°C to 8°C).

6.5 Nature and contents of container

Powder for oral solution: HDPE bottle with child resistant screw cap, fill mark (200 mL of solution after constitution) and measuring cup.
6.6 **Instructions for use/handling**

Constitute with water to a 200 mL deliverable volume solution (stavudine concentration of 1 mg/mL):

1. Add 202 mL of water to the original bottle (when the patient makes up the solution, they should be instructed to fill to the mark). Replace the cap.

2. Shake the bottle well until the powder dissolves completely. The solution may remain slightly hazy.

3. Dispense the solution with the measuring cup provided. The patient should be instructed to shake the bottle well prior to measuring each dose.

7. **MARKETING AUTHORIZATION HOLDER:**

Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom

8. **MARKETING AUTHORIZATION NUMBER(S):**

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:**

10. **DATE OF REVISION OF THE TEXT:**
ANNEX II
MANUFACTURING AUTHORISATIONS AND CONDITIONS OF THE MARKETING AUTHORISATION
1. HOLDERS OF THE MANUFACTURING AUTHORISATIONS

For manufacturing of the active substance, the CPMP identified the following sites:

- Bristol-Myers Squibb Company, Watery Lane, Swords, County Dublin, Ireland.
- Squibb Manufacturing, Inc, P.O. Box 609, State Road No 3, Km 77.5, Humacao 00792 Puerto Rico.

There was no request from the CPMP to conduct inspections of these manufacturing sites.

Manufacturer of the finished product, Zerit® capsules

- Bristol-Myers Squibb, Rue du Docteur Gilles, 28231 Epernon, France.
  (Authorisation issued by the French Medicines Agency on 17/02/1993).
  GMP certificate was issued by the French Authorities on 28 February 1995.

Manufacturer of the finished product, Zerit®, powder for oral solution:

- Bristol-Myers Squibb Company, 2400 W. Lloyd Expressway, Evansville, Indiana 47721, United States of America.

Following the discussion at the September CPMP meeting, an inspection of this manufacturing site was required. This facility has been inspected by the Swedish Inspection Authorities in association with the French Inspection Authorities on 7-10 November 1995 and has been found satisfactory.

Manufacturer responsible for the batch release in the EU:

- Bristol-Myers Squibb, Rue du Docteur Gilles, 28231 Epernon, France.
  (Authorisation delivered by the French Medicines Agency on 17/02/1993).
  GMP certificate was issued by the French Authorities on 28 February 1995.

2. CONDITIONS OR RESTRICTIONS OF SUPPLY AND USE

Medicinal product subject to restricted non-renewable medical prescription.

3. SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDER

3.1 The company, after having been consulted (letters dated on 16 January 1996 and letter dated on 18 January 1996) agreed to fulfil the commitment to submit to the EMEA, within the specific time-frame, the results of the additional studies set out below.

- Results on the two-year ongoing carcinogenicity study carried out in rats and mice will be submitted by the company by 31 December 1996 (CPMP/057/96).
- The company will provide by 31 March 1996 a chromatographic method for the identification of the main components of the spray dried cherry flavour (FMC # 20194), (CPMP/058/96).
• The company has agreed to provide by 31 May 1996 proposed strategies to evaluate the incidence of pneumocystis carinii pneumonia (PCP) in patients on stavudine therapy and possible interactions with PCP prophylactic agents (CPMP/091/96).

3.2. The company has provided a description of the ongoing clinical trials with stavudine in combination therapy and in children (CPMP/059/96, letter dated on 17 January 1996). The company agrees to inform the EMEA on the important new data when available.
ANNEX III
LABELLING AND USER PACKAGE LEAFLET
A - LABELLING
ZERIT®
(stavudine)

Capsules - 15 mg

For oral use

Each capsule contains: stavudine 15 mg, lactose and colorants (E171, E172)

Marketing authorisation holder:

Marketing authorisation number:

Batch number:

Expiry date:

Before use, please see user package leaflet

Keep out of reach of children

Medicinal product subject to medical prescription
ZERIT®
(stavudine)

Capsules - 20 mg

For oral use

Each capsule contains: stavudine 20 mg, lactose and colorants (E171, E172)

Marketing authorisation holder:

Marketing authorisation number:

Batch number:

Expiry date:

Before use, please see user package leaflet

Keep out of reach of children

Medicinal product subject to medical prescription
ZEKIT®
(stavudine)

Capsules - 30 mg

For oral use

Each capsule contains: stavudine 30 mg, lactose and colorants (E171, E172)

Marketing authorisation holder:

Marketing authorisation number:

Batch number:

Expiry date:

Before use, please see user package leaflet

Keep out of reach of children

Medicinal product subject to medical prescription
ZEROIT©
(stavudine)

Capsules - 40 mg

For oral use

Each capsule contains: stavudine 40 mg, lactose and colorants (E171, E172)

Marketing authorisation holder:

Marketing authorisation number:

Batch number:

Expiry date:

Before use, please see user package leaflet

Keep out of reach of children

Medicinal product subject to medical prescription
Packaging text
Powder for oral solution

ZERIT®
(stavudine)

Powder for Oral Solution

For oral use

When prepared as directed, each mL contains 1 mg stavudine, 50 mg sucrose, and preservatives (E218 and E216):

Marketing authorisation holder:

Marketing authorization number:

Batch number:

Expiry date:

Before use, please see user package leaflet

Date of constitution

Stable for 30 days after constitution, when stored in a refrigerator (2-8°C)

Shake well before use:

Keep out of reach of children

200 mL suspension

Medicinal product subject to medical prescription
B.- USER PACKAGE LEAFLET
If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

COMPOSITION
The active ingredient in these capsules is stavudine. Each capsule contains 15 mg of stavudine per capsule, with 60 capsules per bottle, or 56 capsules per carton.

The other ingredients are: lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171).

To help protect the capsules from excessive moisture, the bottle includes a dessicant cannister. The markings on the capsules are in edible printing ink.

TYPE OF MEDICINE: stavudine is an antiviral agent for the treatment of infection with the Human Immunodeficiency Virus (HIV).

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom

MANUFACTURER: Bristol-Myers Squibb, rue du Dr. Gilles, F-28260 Epernon, France

WHEN SHOULD ZERIT® BE USED?
Zerit® is used in the treatment of HIV infection.

WHEN SHOULD ZERIT® NOT BE USED?
Do not take this medicine if you are allergic to stavudine or any of the other ingredients (see Composition). Contact your doctor or pharmacist for advice.

IMPORTANT INFORMATION BEFORE TAKING ZERIT®
There are certain conditions which you may have, or have had, which require special care before or while taking Zerit®. Therefore, before using this medicine, you should have told your doctor if you suffer from kidney disease, if you have had peripheral neuropathy (persistent tingling, or numbness or pain in the feet and/or hands), or if you suffered from pancreatitis.

PREGNANCY AND BREAST FEEDING
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

INTERACTIONS WITH OTHER MEDICINES
Do not take any other medicines while you are taking Zerit®, unless you have told your doctor or pharmacist and asked for their advice.

ZERIT®, DRIVING AND OPERATING MACHINERY
The use of Zerit® by itself should not affect your ability to drive, nor operate machinery.
SPECIAL WARNINGS
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Zerit® may improve your condition, but you will remain infectious while taking it. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections, linked to your weakened immunity (opportunistic infections) may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Zerit®.

You should contact your doctor if the following develops: persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), or abdominal pain, nausea or vomiting (which may indicate pancreatitis or liver disturbance).

At present, there is insufficient information to recommend the use of stavudine in children under the age of 12 years.

These capsules contain lactose, but even in patients with lactose intolerance this quantity is probably not sufficient to induce specific symptoms of intolerance.

HOW TO TAKE ZERIT®
Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely and do not change the dose on your own. The usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose). The capsules should be swallowed with at least 100 mL of water, at least one hour before a meal.

DURATION OF TREATMENT
Continue to take this medicine until your doctor tells you otherwise.

MISSING A DOSE
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not double the dose to make up for the one missed.

OVERDOSE
There is no immediate danger if you have taken too many capsules or if someone (eg. a child) accidentally swallows some. Contact your doctor (or the nearest hospital) for advice.

UNDESIRABLE EFFECTS
All medicines may cause some unwanted or side-effects. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit®, by any other medicines you take at the same time, or by complications of the infection.

Apart from peripheral neuropathy, pancreatitis and liver disturbances (see Special Warnings) other unwanted effects have been reported: malaise, nausea/vomiting, indigestion, diarrhoea or constipation, shortness of breath, respiratory infection, chills/fever and sweating, dizziness, headache, flu-like symptoms and general weakness, rash, allergic reactions, loss of appetite, abdominal-, chest-, muscle- and joint pain, pain, sleeping problems, mood disturbances, and disorders of blood, nerves and lymph nodes.

If you experience any other unusual symptoms, please tell your doctor or pharmacist.

HOW TO STORE ZERIT®
As with other medicines, this product should be stored where children cannot reach it (eg. in a locked cupboard or medicine cabinet). The capsules should be stored at room temperature (15-30°C). They should not get too hot or damp; so do not leave them near a radiator, on a window sill or in the bathroom.
You will see an "EXPIRY DATE" on the bottle, on the blister and on the carton. Do not use the capsules after this date.

DATE OF LAST REVISION:
OTHER INFORMATION:

For any information about this product please contact the local representative of the marketing authorization holder:

**United Kingdom:** 141-149 Staines Road, Hounslow, Middlesex TW3 3JA
Tel: 44 181 754 35 90

**Ireland:** Watery Lane, Swords, Co. Dublin,
Tel: 353 1840 62 44

**Austria:** Colombusgasse 4, 1100 Wien
Tel: 43 1 60 14 327

**Belgium:** Waterloo Office Park, Dreve Richelle 161,B1410 Waterloo
Tel: 32 2 352 74 60

**Denmark:** Jaegersborvej 64-66, 2800 Lyngby
Tel: 45 93 05 06

**Finland:** Valkjärventie 2, 02130 Espoo
Tel: 358 90 435 77 300

**France:** Immeuble Vendome A, Quartier La Grande Arche-Cedex 24, Les Collines de L’Arche, 92057 Paris La Défense Cedex
Tel: 33 1 40 90 60 00

**Germany:** Volkartstrasse 83, 80636 Munchen
Tel: 49 89 12 14 20

**Greece:** 11th Km, Athens-Lamia National Road, 14451 Metamorphosis, Athens
Tel: 30 1 281 67 46

**Italy:** Via Paolo di Dona 73, 00142 Rome
Tel: 39 6 503 96 330

**Luxembourg:** see Belgium

**The Netherlands:** Vijzelmolenlaan 4, 3447 GX Woerden
Tel: 31 34 807 42 22

**Portugal:** Edificio América, Escritoria 29, 1600 Lisbon
Tel: 351 1 79 39 641

**Spain:** Plaza Pablo Ruiz Picasso S/N, Plantas 39-40, 28020 Madrid
Tel: 34 1 582 11 63

**Sweden:** Gustavslundsvagen 145, 161 15 Bromma
Tel: 46 8 704 71 00
ZERIT® (stavudine)
20 mg capsules

USER PACKAGE LEAFLET

If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

COMPOSITION
The active ingredient in these capsules is stavudine. Each capsule contains 20 mg of stavudine per capsule, with 60 capsules per bottle, or 56 capsules per carton.

The other ingredients are: lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171).

To help protect the capsules from excessive moisture, the bottle includes a dessicant cannister. The markings on the capsules are in edible printing ink.

TYPE OF MEDICINE: stavudine is an antiviral agent for the treatment of infection with the Human Immunodeficiency Virus (HIV).

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom

MANUFACTURER: Bristol-Myers Squibb, rue du Dr. Gilles, F-28260 Epernon, France

WHEN SHOULD ZERIT® BE USED?
Zerit® is used in the treatment of HIV infection.

WHEN SHOULD ZERIT® NOT BE USED?
Do not take this medicine if you are allergic to stavudine or any of the other ingredients (see Composition). Contact your doctor or pharmacist for advice.

IMPORTANT INFORMATION BEFORE TAKING ZERIT®
There are certain conditions which you may have, or have had, which require special care before or while taking Zerit®. Therefore, before using this medicine, you should have told your doctor if you suffer from kidney disease, if you have had peripheral neuropathy (persistent tingling, or numbness or pain in the feet and/or hands), or if you suffered from pancreatitis.

PREGNANCY AND BREAST FEEDING
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

INTERACTIONS WITH OTHER MEDICINES
Do not take any other medicines while you are taking Zerit®, unless you have told your doctor or pharmacist and asked for their advice.

ZERIT®, DRIVING AND OPERATING MACHINERY
The use of Zerit® by itself should not affect your ability to drive, nor operate machinery.
SPECIAL WARNINGS
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Zerit® may improve your condition, but you will remain infectious while taking it. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections, linked to your weakened immunity (opportunistic infections) may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Zerit®.

You should contact your doctor if the following develops: persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), or abdominal pain, nausea or vomiting (which may indicate pancreatitis or liver disturbance).

At present, there is insufficient information to recommend the use of stavudine in children under the age of 12 years.

These capsules contain lactose, but even in patients with lactose intolerance this quantity is probably not sufficient to induce specific symptoms of intolerance.

HOW TO TAKE ZERIT®
Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely and do not change the dose on your own. The usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose). The capsules should be swallowed with at least 100 mL of water, at least one hour before a meal.

DURATION OF TREATMENT
Continue to take this medicine until your doctor tells you otherwise.

MISSING A DOSE
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not double the dose to make up for the one missed.

OVERDOSE
There is no immediate danger if you have taken too many capsules or if someone (eg. a child) accidentally swallows some. Contact your doctor (or the nearest hospital) for advice.

UNDESIRABLE EFFECTS
All medicines may cause some unwanted or side-effects. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit®, by any other medicines you take at the same time, or by complications of the infection.

Apart from peripheral neuropathy, pancreatitis and liver disturbances (see Special Warnings) other unwanted effects have been reported: malaise, nausea/vomiting, indigestion, diarrhoea or constipation, shortness of breath, respiratory infection, chills/fever and sweating, dizziness, headache, flu-like symptoms and general weakness, rash, allergic reactions, loss of appetite, abdominal-, chest-, muscle- and joint pain, pain, sleeping problems, mood disturbances, and disorders of blood, nerves and lymph nodes.

If you experience any other unusual symptoms, please tell your doctor or pharmacist.

HOW TO STORE ZERIT®
As with other medicines, this product should be stored where children cannot reach it (eg. in a locked cupboard or medicine cabinet). The capsules should be stored at room temperature (15-
30°C. They should not get too hot or damp; so do not leave them near a radiator, on a window sill or in the bathroom.

You will see an "EXPIRY DATE" on the bottle, on the blister and on the carton. Do not use the capsules after this date.

DATE OF LAST REVISION:
OTHER INFORMATION:

For any information about this product please contact the local representative of the marketing authorization holder:

**United Kingdom:** 141-149 Staines Road, Hounslow, Middlesex TW3 3JA  
Tel: 44 181 754 35 90

**Ireland:** Watery Lane, Swords, Co. Dublin,  
Tel: 353 1840 62 44

**Austria:** Columbusgasse 4, 1100 Wien  
Tel: 43 1 60 14 327

**Belgium:** Waterloo Office Park, Dreve Richelle 161,B1410 Waterloo  
Tel: 32 2 352 74 60

**Denmark:** Jaegersborvej 64-66, 2800 Lyngby  
Tel: 45 93 05 06

**Finland:** Valkjärventie 2, 02130 Espoo  
Tel: 358 90 435 77 300

**France:** Immeuble Vendome A, Quartier La Grande Arche-Cedex 24, Les Collines de L’Arche, 92057 Paris La Défense Cedex  
Tel: 33 1 40 90 60 00

**Germany:** Volkartstrasse 83, 80636 Munchen  
Tel: 49 89 12 14 20

**Greece:** 11th Km, Athens-Lamia National Road, 14451 Metamorphosis, Athens  
Tel: 30 1 281 67 46

**Italy:** Via Paolo di Dona 73, 00142 Rome  
Tel: 39 6 503 96 330

**Luxembourg:** see Belgium

**The Netherlands:** Vijzelmolenlaan 4, 3447 GX Woerden  
Tel: 31 34 807 42 22

**Portugal:** Edificio América, Escritoria 29, 1600 Lisbon  
Tel: 351 1 79 39 641

**Spain:** Plaza Pablo Ruiz Picasso S/N, Plantas 39-40, 28020 Madrid  
Tel: 34 1 582 11 63

**Sweden:** Gustavslundsvagen 145, 161 15 Bromma  
Tel: 46 8 704 71 00
If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

COMPOSITION
The active ingredient in these capsules is stavudine. Each capsule contains 30 mg of stavudine per capsule, with 60 capsules per bottle, or 56 capsules per carton.

The other ingredients are: lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171).

To help protect the capsules from excessive moisture, the bottle includes a dessicant cannister. The markings on the capsules are in edible printing ink.

TYPE OF MEDICINE: stavudine is an antiviral agent for the treatment of infection with the Human Immunodeficiency Virus (HIV).

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom

MANUFACTURER: Bristol-Myers Squibb, rue du Dr. Gilles, F-28260 Epernon, France

WHEN SHOULD ZERIT® BE USED?
Zerit® is used in the treatment of HIV infection.

WHEN SHOULD ZERIT® NOT BE USED?
Do not take this medicine if you are allergic to stavudine or any of the other ingredients (see Composition). Contact your doctor or pharmacist for advice.

IMPORTANT INFORMATION BEFORE TAKING ZERIT®
There are certain conditions which you may have, or have had, which require special care before or while taking Zerit®. Therefore, before using this medicine, you should have told your doctor if you suffer from kidney disease, if you have had peripheral neuropathy (persistent tingling, or numbness or pain in the feet and/or hands), or if you suffered from pancreatitis.

PREGNANCY AND BREAST FEEDING
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

INTERACTIONS WITH OTHER MEDICINES
Do not take any other medicines while you are taking Zerit®, unless you have told your doctor or pharmacist and asked for their advice.

ZERIT®, DRIVING AND OPERATING MACHINERY
The use of Zerit® by itself should not affect your ability to drive, nor operate machinery.
SPECIAL WARNINGS
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Zerit® may improve your condition, but you will remain infectious while taking it. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections, linked to your weakened immunity (opportunistic infections) may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Zerit®.

You should contact your doctor if the following develops: persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), or abdominal pain, nausea or vomiting (which may indicate pancreatitis or liver disturbance).

At present, there is insufficient information to recommend the use of stavudine in children under the age of 12 years.

These capsules contain lactose, but even in patients with lactose intolerance this quantity is probably not sufficient to induce specific symptoms of intolerance.

HOW TO TAKE ZERIT®
Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely and do not change the dose on your own. The usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose). The capsules should be swallowed with at least 100 mL of water, at least one hour before a meal.

DURATION OF TREATMENT
Continue to take this medicine until your doctor tells you otherwise.

MISSING A DOSE
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not double the dose to make up for the one missed.

OVERDOSE
There is no immediate danger if you have taken too many capsules or if someone (eg. a child) accidentally swallows some. Contact your doctor (or the nearest hospital) for advice.

UNDESIRABLE EFFECTS
All medicines may cause some unwanted or side-effects. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit®, by any other medicines you take at the same time, or by complications of the infection.

Apart from peripheral neuropathy, pancreatitis and liver disturbances (see Special Warnings) other unwanted effects have been reported: malaise, nausea/vomiting, indigestion, diarrhoea or constipation, shortness of breath, respiratory infection, chills/fever and sweating, dizziness, headache, flu-like symptoms and general weakness, rash, allergic reactions, loss of appetite, abdominal-, chest-, muscle- and joint pain, pain, sleeping problems, mood disturbances, and disorders of blood, nerves and lymph nodes.

If you experience any other unusual symptoms, please tell your doctor or pharmacist.

HOW TO STORE ZERIT®
As with other medicines, this product should be stored where children cannot reach it (eg. in a locked cupboard or medicine cabinet). The capsules should be stored at room temperature (15-
30°C). They should not get too hot or damp; so do not leave them near a radiator, on a window sill or in the bathroom.

You will see an "EXPIRY DATE" on the bottle, on the blister and on the carton. Do not use the capsules after this date.

DATE OF LAST REVISION:
OTHER INFORMATION:

For any information about this product please contact the local representative of the marketing authorization holder:

United Kingdom: 141-149 Staines Road, Hounslow, Middlesex TW3 3JA
Tel: 44 181 754 35 90

Ireland: Watery Lane, Swords, Co. Dublin,
Tel: 353 1840 62 44

Austria: Columbusgasse 4, 1100 Wien
Tel: 43 1 60 14 327

Belgium: Waterloo Office Park, Dreve Richelle 161,B1410 Waterloo
Tel: 32 2 352 74 60

Denmark: Jaegersborvej 64-66, 2800 Lyngby
Tel: 45 93 05 06

Finland: Valkjärventie 2, 02130 Espoo
Tel: 358 90 435 77 300

France: Immeuble Vendome A, Quartier La Grande Arche-Cedex 24, Les Collines de L’Arche, 92057 Paris La Défense Cedex
Tel: 33 1 40 90 60 00

Germany: Volkartstrasse 83, 80636 Munchen
Tel: 49 89 12 14 20

Greece: 11th Km, Athens-Lamia National Road, 14451 Metamorphosis, Athens
Tel: 30 1 281 67 46

Italy: Via Paolo di Dona 73, 00142 Rome
Tel: 39 6 503 96 330

Luxembourg: see Belgium

The Netherlands: Vijzelmolenlaan 4, 3447 GX Woerden
Tel: 31 34 807 42 22

Portugal: Edificio América, Escritoria 29, 1600 Lisbon
Tel: 351 1 79 39 641

Spain: Plaza Pablo Ruiz Picasso S/N, Plantas 39-40, 28020 Madrid
Tel: 34 1 582 11 63

Sweden: Gustavslundsvagen 145, 161 15 Bromma
Tel: 46 8 704 71 00
ZERIT® (stavudine)
40 mg capsules

USER PACKAGE LEAFLET

If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

COMPOSITION
The active ingredient in these capsules is stavudine. Each capsule contains 40 mg of stavudine per capsule, with 60 capsules per bottle, or 56 capsules per carton.

The other ingredients are: lactose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The capsule shell is composed of gelatin, iron oxide colorant (E172), silicon dioxide, sodium lauryl sulphate and titanium dioxide colorant (E171).

To help protect the capsules from excessive moisture, the bottle includes a dessicant cannister. The markings on the capsules are in edible printing ink.

TYPE OF MEDICINE: stavudine is an antiviral agent for the treatment of infection with the Human Immunodeficiency Virus (HIV).

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom

MANUFACTURER: Bristol-Myers Squibb, rue du Dr. Gilles, F-28260 Epernon, France

WHEN SHOULD ZERIT® BE USED?
Zerit® is used in the treatment of HIV infection.

WHEN SHOULD ZERIT® NOT BE USED?
Do not take this medicine if you are allergic to stavudine or any of the other ingredients (see Composition). Contact your doctor or pharmacist for advice.

IMPORTANT INFORMATION BEFORE TAKING ZERIT®
There are certain conditions which you may have, or have had, which require special care before or while taking Zerit®. Therefore, before using this medicine, you should have told your doctor if you suffer from kidney disease, if you have had peripheral neuropathy (persistent tingling, or numbness or pain in the feet and/or hands), or if you suffered from pancreatitis.

PREGNANCY AND BREAST FEEDING
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

INTERACTIONS WITH OTHER MEDICINES
Do not take any other medicines while you are taking Zerit®, unless you have told your doctor or pharmacist and asked for their advice.

ZERIT®, DRIVING AND OPERATING MACHINERY
The use of Zerit® by itself should not affect your ability to drive, nor operate machinery.
SPECIAL WARNINGS
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Zerit® may improve your condition, but you will remain infectious while taking it. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections, linked to your weakened immunity (opportunistic infections) may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Zerit®.

You should contact your doctor if the following develops: persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), or abdominal pain, nausea or vomiting (which may indicate pancreatitis or liver disturbance).

At present, there is insufficient information to recommend the use of stavudine in children under the age of 12 years.

These capsules contain lactose, but even in patients with lactose intolerance this quantity is probably not sufficient to induce specific symptoms of intolerance.

HOW TO TAKE ZERIT®
Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely and do not change the dose on your own. The usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose). The capsules should be swallowed with at least 100 mL of water, at least one hour before a meal.

DURATION OF TREATMENT
Continue to take this medicine until your doctor tells you otherwise.

MISSING A DOSE
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not double the dose to make up for the one missed.

OVERDOSE
There is no immediate danger if you have taken too many capsules or if someone (eg. a child) accidentally swallows some. Contact your doctor (or the nearest hospital) for advice.

UNDESIRABLE EFFECTS
All medicines may cause some unwanted or side-effects. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit®, by any other medicines you take at the same time, or by complications of the infection.

Apart from peripheral neuropathy, pancreatitis and liver disturbances (see Special Warnings) other unwanted effects have been reported: malaise, nausea/vomiting, indigestion, diarrhoea or constipation, shortness of breath, respiratory infection, chills/fever and sweating, dizziness, headache, flu-like symptoms and general weakness, rash, allergic reactions, loss of appetite, abdominal-, chest-, muscle- and joint pain, pain, sleeping problems, mood disturbances, and disorders of blood, nerves and lymph nodes.

If you experience any other unusual symptoms, please tell your doctor or pharmacist.

HOW TO STORE ZERIT®
As with other medicines, this product should be stored where children cannot reach it (eg. in a locked cupboard or medicine cabinet). The capsules should be stored at room temperature (15-
30°C). They should not get too hot or damp; so do not leave them near a radiator, on a window sill or in the bathroom.

You will see an "EXPIRY DATE" on the bottle, on the blister and on the carton. Do not use the capsules after this date.

DATE OF LAST REVISION:
OTHER INFORMATION:

For any information about this product please contact the local representative of the marketing authorization holder:

United Kingdom: 141-149 Staines Road, Hounslow, Middlesex TW3 3JA
Tel: 44 181 754 35 90

Ireland: Watery Lane, Swords, Co. Dublin,
Tel: 353 1840 62 44

Austria: Colombusgasse 4, 1100 Wien
Tel: 43 1 60 14 327

Belgium: Waterloo Office Park, Dreve Richelle 161,B1410 Waterloo
Tel: 32 2 352 74 60

Denmark: Jaegersborvej 64-66, 2800 Lyngby
Tel: 45 93 05 06

Finland: Valkjärventie 2, 02130 Espoo
Tel: 358 90 435 77 300

France: Immeuble Vendome A, Quartier La Grande Arche-Cedex 24, Les
Collines de L’Arche, 92057 Paris La Défense Cedex
Tel: 33 1 40 90 60 00

Germany: Volkartstrasse 83, 80636 Munchen
Tel: 49 89 12 14 20

Greece: 11th Km, Athens-Lamia National Road, 14451 Metamorphosis, Athens
Tel: 30 1 281 67 46

Italy: Via Paolo di Dona 73, 00142 Rome
Tel: 39 6 503 96 330

Luxembourg: see Belgium

The Netherlands: Vijzelmolenlaan 4, 3447 GX Woerden
Tel: 31 34 807 42 22

Portugal: Edificio América, Escritoria 29, 1600 Lisbon
Tel: 351 1 79 39 641

Spain: Plaza Pablo Ruiz Picasso S/N, Plantas 39-40, 28020 Madrid
Tel: 34 1 582 11 63

Sweden: Gustavslundsvagen 145, 161 15 Bromma
Tel: 46 8 704 71 00
**ZERIT® ( stavudine) **

*Powder for oral solution*

**USER PACKAGE LEAFLET**

*If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.*

**COMPOSITION**
The active ingredient is *stavudine*. After constitution with water, each bottle contains 200 mg stavudine as a 1 mg/mL solution.

The other ingredients are: cherry flavour, methylparaben preservative (E218), propylparaben preservative (E216), silicon dioxide, simethicone, sodium carboxymethylcellulose, sorbic acid, stearate emulsifiers and sucrose.

**TYPE OF MEDICINE:** Stavudine is an antiviral agent for the treatment of infection with the Human Immunodeficiency Virus (HIV).

**MARKETING AUTHORISATION HOLDER:** Bristol-Myers Squibb Pharma EEIG, Swakeleys House, Milton Road, Ickenham UB10 8PU, United Kingdom.

**MANUFACTURER:** Bristol-Myers Squibb, rue du Docteur Gilles, F-28260 Epernon, France

**WHEN SHOULD ZERIT® BE USED?**
Zerit® is used in the treatment of HIV infection.

**WHEN SHOULD ZERIT® NOT BE USED?**
Do not take this medicine if you are allergic to stavudine or any of the other ingredients (see Composition). Contact your doctor or pharmacist for advice.

**IMPORTANT INFORMATION BEFORE TAKING ZERIT®**
There are certain conditions which you may have, or have had, which require special care before or while taking Zerit®. Therefore, before using this medicine, you should have told your doctor if you suffer from kidney disease, if you have had peripheral neuropathy (persistent tingling, or numbness or pain in the feet and/or hands), or if you suffered from pancreatitis.

**PREGNANCY AND BREAST FEEDING**
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

**INTERACTIONS WITH OTHER MEDICINES**
Do not take any other medicines while you are taking Zerit®, unless you have told your doctor or pharmacist and asked for their advice.

**ZERIT®, DRIVING AND OPERATING MACHINERY**
The use of Zerit® by itself should not affect your ability to drive, nor operate machinery.
SPECIAL WARNINGS
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Zerit® may improve your condition, but you will remain infectious while taking it. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections linked to your weakened immunity (opportunistic infections), may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Zerit®.

You should contact your doctor if the following develops: persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), or abdominal pain, nausea or vomiting (which may indicate pancreatitis or liver disturbance).

At present, there is insufficient information to recommend the use of stavudine in children under the age of 12 years.

Diabetic patients: after constitution with water, the solution will contain 50 mg of sucrose per mL of solution.

HOW TO TAKE ZERIT®
Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely and do not change the dose on your own. The usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose), at least one hour before a meal.

Prepare the ready-to-use solution by mixing the powder with 202 ml of water or by slowly adding water up to the fill mark on the bottle. Then screw the cap on tightly and shake the bottle well until the powder dissolves completely, and take or dispense the solution with the measuring cup provided. Do not worry if the solution remains slightly hazy after mixing with water; this is normal. If needed, consult your pharmacist for help with this procedure.

DURATION OF TREATMENT
Continue to take this medicine until your doctor tells you otherwise.

MISSING A DOSE
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not double the dose to make up for the one missed.

OVERDOSE
There is no immediate danger if you have taken too much of the solution, or if it was accidentally taken by someone (eg. a child). Contact your doctor (or the nearest hospital) for advice.

UNDESIRABLE EFFECTS
All medicines may cause some unwanted or side-effects. When treating HIV infection it is not always possible to differentiate between unwanted effects caused by Zerit® by any other medicines you take at the same time, or by the complications of the infection.

Apart from peripheral neuropathy, pancreatitis and liver disturbances (see Special Warnings) other unwanted effects have been reported: malaise, nausea/vomiting, indigestion, diarrhoea or constipation, shortness of breath, respiratory infection, chills/fever and sweating, dizziness, headache, flu-like symptoms and general weakness, rash, allergic reactions, loss of appetite, abdominal-, chest-, muscle- and joint pain, pain, sleeping problems, mood disturbances, and disorders of blood, nerves and lymph nodes.
If you experience any other unusual symptoms, tell your doctor or pharmacist.

HOW TO STORE ZERIT®
As any other medicine, this product should be stored where children cannot reach it (e.g., in a locked cupboard or medicine cabinet). The dry powder should be stored at room temperature (15-30°C) in the original bottle. It should not get too hot or damp; so do not leave the bottle near a radiator, on a window sill or in the bathroom. Following preparation of the ready-to-use solution, this should be stored in a refrigerator (not in a freezer), but for not more than 30 days (2°C-8°C).

You will see an "EXPIRY DATE" on the bottle and on the carton. Do not use the powder after this date.

DATE OF LAST REVISION:
OTHER INFORMATION:

For any information about this product please contact the local representative of the marketing authorization holder:

**United Kingdom:** 141-149 Staines Road, Hounslow, Middlesex TW3 3JA  
Tel: 44 181 754 35 90

**Ireland:** Watery Lane, Swords, Co. Dublin,  
Tel: 353 1840 62 44

**Austria:** Columbusgasse 4, 1100 Wien  
Tel: 43 1 60 14 327

**Belgium:** Waterloo Office Park, Dreve Richelle 161,B1410 Waterloo  
Tel: 32 2 352 74 60

**Denmark:** Jaegersborvej 64-66, 2800 Lyngby  
Tel: 45 93 05 06

**Finland:** Valkjärventie 2, 02130 Espoo  
Tel: 358 90 435 77 300

**France:** Immeuble Vendome A, Quartier La Grande Arche-Cedex 24, Les Collines de L’Arche, 92057 Paris La Défense Cedex  
Tel: 33 1 40 90 60 00

**Germany:** Volkartstrasse 83, 80636 Munchen  
Tel: 49 89 12 14 20

**Greece:** 11th Km, Athens-Lamia National Road, 14451 Metamorphosis, Athens  
Tel: 30 1 281 67 46

**Italy:** Via Paolo di Dona 73, 00142 Rome  
Tel: 39 6 503 96 330

**Luxembourg:** see Belgium

**The Netherlands:** Vijzelmolenlaan 4, 3447 GX Woerden  
Tel: 31 34 807 42 22

**Portugal:** Edificio América, Escritoria 29, 1600 Lisbon  
Tel: 351 1 79 39 641

**Spain:** Plaza Pablo Ruiz Picasso S/N, Plantas 39-40, 28020 Madrid  
Tel: 34 1 582 11 63

**Sweden:** Gustavslundsvagen 145, 161 15 Bromma  
Tel: 46 8 704 71 00