

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **CAELYX**[®]

Pegylated Liposomal Doxorubicin Hydrochloride for Injection
Suspension, 2 mg/mL, for intravenous administration
Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

| | |
|--|---------|
| 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential | 03/2024 |
| 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 pregnant Women | 03/2024 |
| 7 WARNINGS AND PRECAUTIONS, Respiratory | 03/2024 |

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CAELYX (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is indicated for:

- monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk associated with conventional doxorubicin.
- Advanced ovarian carcinoma in women who have failed standard first-line therapy. Platinum-and paclitaxel- based chemotherapy is the current standard first-line treatment regimen.
- AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm³) and extensive mucocutaneous or visceral disease whose disease has progressed despite therapy or who are intolerant to prior systemic combination chemotherapy comprising of at least two of the following agents: a vinca alkaloid, bleomycin and doxorubicin (or another anthracycline).

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>60 years): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Experience with CAELYX in geriatrics patients is limited (see [10.3 Pharmacokinetics](#)).

2 CONTRAINDICATIONS

- CAELYX is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- Should not be administered while breast-feeding (see [7.1.2 Breast-feeding](#)).
- Should not be administered in pregnant women (see [7.1.1 Pregnant Women](#), and [7 Warnings and Precautions, Teratogenicity](#))

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

| |
|---|
| Serious Warnings and Precautions |
|---|

- Cardiotoxicity including congestive heart failure and cardiomyopathy may occur (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#));
- Acute infusion reactions (see [7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions](#));
- Myelosuppression (see [7 WARNINGS AND PRECAUTIONS, Hematologic](#));
- Secondary oral neoplasms including fatal cases (see [7 WARNINGS AND PRECAUTIONS, Second Primary Malignancies](#))
- CAELYX should only be administered by physicians experienced with cancer chemotherapeutic drugs.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

CAELYX (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use.

Breast Cancer/Ovarian Cancer Patients

CAELYX is administered intravenously at a dose of 50 mg/m² body surface, once every 4 weeks for as long as the disease does not progress, and the patient shows no evidence of clinical cardiotoxicity and continues to tolerate treatment.

For doses < 90 mg: dilute CAELYX in 250 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.

For doses ≥ 90 mg: dilute CAELYX in 500 mL (50 mg/mL) (5%) Dextrose USP solution for infusion.

The use of any diluent other than Dextrose 5% in water for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol, may cause precipitation of CAELYX.

To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent CAELYX infusions may be administered over a 60-minute period.

In the breast cancer trial program, modification of the infusion was permitted for those patients experiencing an infusion reaction as follows:

5% of the total dose was infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate was doubled for the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes.

Subsequent CAELYX infusions may be administered over a 60-minute period.

Serious and sometimes life-threatening infusion reactions, which are characterized by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial edema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of CAELYX (see [7 WARNINGS AND PRECAUTIONS](#)). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, and adrenaline) as well as emergency equipment should be available for immediate use. In most patients, treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimize the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute.

AIDS-KS Patients

CAELYX should be administered intravenously at a dose of 20 mg/m² body surface (equivalent to doxorubicin hydrochloride) once every two- to- three weeks. Intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out. Patients should be treated for as long as they respond satisfactorily and tolerate treatment.

The appropriate dose of CAELYX is diluted in 250 mL of (5%) Dextrose Injection USP and administered by intravenous infusion over 30 minutes. CAELYX should not exceed 90 mg per infusion. Rapid infusion may increase the risk of infusion-related reactions (see [7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions](#)). It is recommended that the CAELYX infusion line be connected through the side port of an intravenous infusion of (5%) Dextrose USP Intravenous Infusion to achieve further dilution and minimize the risk of thrombosis and extravasation.

CAELYX should be considered an irritant and precautions should be taken to avoid extravasation. On intravenous administration of CAELYX, extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

Dose Modifications

Dose adjustment is required in patients with a history of prior anthracycline use, prior mediastinal irradiation, concurrent cyclophosphamide therapy, and pre-existing cardiovascular disease.

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or hematologic toxicity, the dose may be reduced or delayed. Guidelines for CAELYX dose modification secondary to these adverse effects are provided in the following tables. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE and stomatitis (Table 1, Table 2) provide the schedule followed for dose modification in clinical trials in the treatment of breast cancer or ovarian cancer (modification of the recommended 4-week treatment cycle). If these toxicities occur in patients with AIDS-related KS, the recommended 2- to 3-week treatment cycle can be modified in a similar manner.

The table for hematological toxicity (Table 3) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in Table 4, Table 5, and Table 6.

Guidelines for CAELYX Dose Modification in Breast or Ovarian Cancer Patients

| Table 1 - PALMAR - PLANTAR ERYTHRODYSESTHESIA | | |
|--|--|---|
| Toxicity Grade At Current Assessment | Week After Prior CAELYX Dose | |
| | Weeks 4 & 5 | Week 6 |
| Grade -1- (mild erythema, swelling, or desquamation not interfering with daily activities) | Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week | Decrease dose by 25%; return to 4-week interval |
| Grade -2- (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter) | Wait an additional week | Decrease dose by 25%; return to 4-week interval |
| Grade -3- (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing) | Wait an additional week | Withdraw patient |
| Grade -4- (diffuse or local process causing infectious complications, or a bedridden state or hospitalization) | Wait an additional week | Withdraw patient |

| Table 2 - STOMATITIS | | |
|---|--|--|
| | Week after Prior CAELYX Dose | |
| Toxicity Grade at Current Assessment | Weeks 4 & 5 | Week 6 |
| Grade -1- (painless ulcers, erythema, or mild soreness) | Redose unless patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week | Decrease dose by 25%; return to 4-week interval or withdraw patient per physician's assessment |
| Grade -2- (painful erythema, edema, or ulcers, but can eat) | Wait an additional week | Decrease dose by 25%; return to 4-week interval or withdraw patient per physician's assessment |
| Grade -3- (painful erythema, edema, or ulcers, but cannot eat) | Wait an additional week | Withdraw patient |
| Grade -4- (requires parenteral or enteral support) | Wait an additional week | Withdraw patient |

| Table 3 - HEMATOLOGICAL TOXICITY (ANC OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER | | | |
|---|--------------|------------------|---|
| GRADE | ANC | PLATELETS | MODIFICATION |
| 1 | 1500 - 1900 | 75,000 - 150,000 | Resume treatment with no dose reduction. |
| 2 | 1000 - <1500 | 50,000 - <75,000 | Wait until ANC \geq 1,500 and platelets \geq 75,000; redose with no dose reduction. |
| 3 | 500 - <1000 | 25,000 - <50,000 | Wait until ANC \geq 1,500 and platelets \geq 75,000; redose with no dose reduction. |
| 4 | <500 | <25,000 | Wait until ANC \geq 1,500 and platelets \geq 75,000; decrease dose by 25% or continue full dose with growth factor support. |

The dose modifications shown in the tables below are recommended for managing possible adverse events in AIDS-KS patients:

Guidelines for CAELYX Dose Modification in AIDS-KS Patients

| Table 4 - PALMAR-PLANTAR ERYTHRODYSESTHESIA | | |
|--|--|------------------------------|
| Toxicity | | Weeks Since Last Dose |
| | | |

| Grade | Symptoms | 3 | 4 |
|-------|---|---|---|
| 0 | no symptoms | Redose at 2-to 3-week interval | Redose at 2-to 3-week interval |
| 1 | mild erythema, swelling, or desquamation not interfering with daily activities | Redose unless patient has experienced a previous grade 3 or 4 skin toxicity in which case wait an additional week | Redose at 25% dose reduction; return to 3-week interval |
| 2 | erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter | Wait an additional week | Redose at 50% dose reduction; return to 3-week interval |
| 3 | blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing | Wait an additional week | Discontinue CAELYX |
| 4 | diffuse or local process causing infectious complications, or a bed ridden state or hospitalization | | |

| Grade | ANC (10 ⁹ cells/L) | Platelets (10 ⁹ cells/L) | Modification |
|-------|-------------------------------|-------------------------------------|--|
| 1 | 1.5 - 1.9 | 75 - 150 | None |
| 2 | 1.0 - <1.5 | 50 - <75 | None |
| 3 | 0.5 - 0.999 | 25 - <50 | Wait until ANC ≥1.0 and/or platelets ≥50 then redose at 25% dose reduction |
| 4 | <0.5 | <25 | Wait until ANC ≥1.0 and/or platelets ≥50 then redose at 50% dose reduction |

| Grade | Symptoms | Modification |
|-------|--|--|
| 1 | Painless ulcers, erythema, or mild soreness | None |
| 2 | Painful erythema, edema, or ulcers, but can eat | Wait one week and if symptoms improve redose at 100% dose |
| 3 | Painful erythema, edema, or ulcers, and cannot eat | Wait one week and if symptoms improve redose at 25% dose reduction |

| | | |
|---|--|--|
| 4 | Requires parenteral or enteral support | Wait one week and if symptoms improve redose at 50% dose reduction |
|---|--|--|

Patients With Impaired Hepatic Function:

AIDS-KS Patients

Experience with CAELYX in treating AIDS-KS patients with hepatic impairment is limited. Therefore, based on experience with doxorubicin hydrochloride, it is recommended that CAELYX dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 21 to 51 $\mu\text{mol/L}$ (1.2-3.0 mg/dl), give 50% of normal dose; >51 $\mu\text{mol/L}$, give 25% of normal dose.

Breast Cancer/Ovarian Cancer Patients

CAELYX pharmacokinetics determined in a small number of ovarian cancer patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however, until further experience is gained, the CAELYX dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial program as follows:

- At initiation of therapy, if the bilirubin is between 21 to 51 $\mu\text{mol/L}$ (1.2-3.0 mg/dl), the first dose is reduced by 25%.
- If the bilirubin is >51 $\mu\text{mol/L}$ (3.0 mg/dl), the first dose is reduced by 50%.
- If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25% for the first dose, increase to full dose for cycle 2; if reduced by 50% for the first dose, increase to 75% of full dose for cycle 2.
- The dosage can be increased to full dose for subsequent cycles if tolerated.

Prior to CAELYX administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.

Patients With Impaired Renal Function:

As doxorubicin is metabolized by the liver and excreted in the bile, dose modification is not required with CAELYX. Population-based analysis confirms that changes in renal function over the range tested (estimated creatinine clearance 30- 156 mL/min) do not alter the pharmacokinetics of CAELYX. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 mL/min.

AIDS-KS Patients With Splenectomy:

As there is no experience with CAELYX in patients who have had splenectomy, treatment with CAELYX is not recommended.

4.3 Reconstitution

Parenteral Products:

Caution must be exercised in handling CAELYX dispersion. The use of gloves is required. If CAELYX comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. CAELYX must be handled and disposed of in a manner consistent with that of other anticancer medicinal products (see [12 SPECIAL HANDLING INSTRUCTIONS](#)).

Discard CAELYX if it shows evidence of precipitation or any other particulate matter or if it shows a discoloration of the dispersion.

The appropriate dose of CAELYX, up to a maximum of 90 mg, must be diluted in 250 mL of (5%) Dextrose Injection USP, prior to administration. For doses \geq 90 mg, dilute CAELYX in 500 mL of (5%) Dextrose USP Injection, prior to administration.

The reconstituted solution can be stored up to 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C. Partially used vials must be discarded. (see [11 STORAGE, STABILITY AND DISPOSAL](#)).

4.4 Administration

DO NOT administer as a bolus injection or undiluted dispersion. CAELYX must not be given by the intramuscular or subcutaneous route.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in CAELYX.

- Do not use with In-Line Filters.
- Do not mix with other drugs.
- Do not use with any diluent other than (5%) Dextrose Injection USP.
- Do not use any bacteriostatic agent, such as benzyl alcohol.

It is recommended that the CAELYX infusion line be connected through the side port of an intravenous infusion of (50 mg/mL) (5%) Dextrose USP. Infusion may be given through a peripheral vein.

CAELYX is not a clear solution but a translucent, red liposomal dispersion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Do not use material that shows evidence of precipitation or any other particulate matter. Discard unused portion (see [11 STORAGE, STABILITY AND DISPOSAL](#)).

If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short-acting corticosteroid) and restart at a slower rate.

Incompatibility

Until specific compatibility data are available, it is not recommended that CAELYX be mixed with other drugs.

5 OVERDOSAGE

Acute overdosage with doxorubicin hydrochloride causes increases in mucositis, leukopenia and thrombocytopenia.

Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

Chronic overdosage with cumulative doses of doxorubicin hydrochloride exceeding 550 mg/m² body surface, increases the risk of cardiomyopathy and resultant congestive heart failure. Doxorubicin hydrochloride cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of QRS wave, a prolongation of the systolic time interval and a reduction of the left ventricular ejection fraction (LVEF). Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. Reduction of afterload with vasodilating agents has been recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|------------------------------------|---|
| Intravenous Injection | Solution, 2 mg/mL | N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), hydrogenated soy phosphatidylcholine (HSPC), cholesterol, Ammonium sulfate, Histidine, Hydrochloric acid, Sodium hydroxide, Sucrose, and Water for Injection |

CAELYX (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is provided as a sterile, translucent, red liposomal dispersion in 10 mL glass, single-use vials. Vials contain 20 mg doxorubicin hydrochloride in a pegylated liposomal formulation at a concentration of 2 mg/mL in water for injection and a pH of 6.0 - 7.0.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

General

CAELYX should only be administered by physicians experienced with cancer chemotherapeutic drugs.

CAELYX is a unique formulation of doxorubicin hydrochloride and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Infusion Reactions

Serious and sometimes life-threatening infusion reactions may occur within minutes of starting the infusion of CAELYX. These reactions have been described as allergic-like or anaphylactoid-like and are defined by the following COSTART terms: allergic reaction, anaphylactoid reaction, asthma, face edema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnea, pharyngitis, rash, pruritus, sweating, injection site reaction and drug interaction. Very rarely, convulsions have been observed in relation to infusion reactions.

Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medication to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline, and anticonvulsants) as well as emergency equipment should be available for immediate use. In most patients, treatment can be resumed after all symptoms have resolved without recurrence.

Infusion-associated reactions rarely recur after the first treatment cycle. To minimize the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see [4.2 Recommended Dose and Dosage Adjustment](#)).

In patients with solid tumors, 100 out of 929 patients (10.8%) were described as having an infusion-associated reaction during treatment with CAELYX. Permanent treatment discontinuation rates were infrequently reported at 2%.

In the pivotal breast cancer trials, a similar incidence of infusion reactions 32/254 (13%) was observed. The rate of permanent treatment discontinuation was 2% (4/254).

In the ovarian cancer population (subset of the solid tumor cohort), 51/510 (10%) patients reported treatment-related infusion reaction adverse events. Five patients (<1%) (reporting nine events) discontinued due to treatment-related infusion reactions.

In patients with AIDS-KS, infusion-associated reactions were characterized by flushing, shortness of breath, facial edema, headache, chills, back pain, tightness in the chest and throat and/or hypotension and can be expected at the rate of 5% to 10%. Very rarely, convulsions have been observed in relation to infusion reactions. Many patients were able to tolerate further infusions without complications, however, eight patients discontinued CAELYX therapy because of an infusion reaction.

Injection Site Effects

CAELYX should be considered an irritant and precautions should be taken to avoid extravasation (see [4.2 Recommended Dose and Dosage Adjustment](#)).

In studies with rabbits, lesions that were induced by subcutaneous injection of CAELYX were minor and reversible compared to more severe and irreversible lesions and tissue necrosis that were induced after subcutaneous injection of conventional doxorubicin hydrochloride (see [16 NON-CLINICAL TOXICOLOGY](#)).

Toxicity Potentiation

The doxorubicin in CAELYX may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin hydrochloride. Radiation-induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of doxorubicin hydrochloride.

Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY](#).

Cardiovascular

Special attention must be given to the cardiac toxicity exhibited by doxorubicin hydrochloride. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received a total dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m² body surface. This limit appears to be lower (400 mg/m² body surface) in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The incidence of CAELYX-associated cardiotoxicity was significantly lower than that with conventional doxorubicin hydrochloride.

Caution should be observed in patients who have received other anthracyclines or anthracenediones. The total dose of doxorubicin hydrochloride administered to the individual patient should also take into account any previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy.

Patients with a history of cardiovascular disease should be administered CAELYX only when the potential benefit of treatment outweighs the risk.

Cardiac function, particularly left ventricular ejection fraction (LVEF) should be monitored at baseline and periodically by MUGA scan or echography. The evaluation of left ventricular function is considered to be mandatory before each additional administration of CAELYX that exceeds a lifetime cumulative anthracycline dose of 450 mg/m² body surface.

Congestive heart failure and/or cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Hematologic

Hematologic Myelosuppression

In AIDS-KS and other patient populations treated with CAELYX, many patients presented with baseline myelosuppression due to such factors as their HIV disease, numerous concomitant medications, or tumors involving bone marrow. In the AIDS-KS population, myelosuppression appears to be the dose-limiting adverse event. Leukopenia is the most common adverse event (about 60%) experienced in this population; anemia (about 20%) and thrombocytopenia (about 10%) can also be expected.

In patients with ovarian cancer treated at a dose of 50 mg/m² body surface, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropenic infection or sepsis. A similar low incidence of myelosuppression was seen in patients with metastatic breast cancer receiving CAELYX in a first-line clinical trial, although febrile neutropenia was seen in 3/254 (1.2 %) patients receiving CAELYX 50 mg/m² body surface, every 4 weeks.

Leukopenia (33.2%) was the most frequently reported hematological adverse event, followed by anemia (32.2%), neutropenia (31.6%) and thrombocytopenia (10.7%). Life-threatening (Grade IV) hematological effects were extremely rare (1.6%, 0.4%, 2.9% and 0.2% respectively). Growth factor support was required infrequently (<5%) and transfusion support was required in approximately 15% of patients.

Because of this potential for bone marrow suppression, careful hematologic monitoring is required during use of CAELYX. Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of CAELYX. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or suspension or delay of CAELYX therapy.

Persistent severe myelosuppression, although not seen in patients with breast or ovarian cancer, may result in superinfection or hemorrhage.

CAELYX may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when CAELYX is administered in combination with other agents that cause bone marrow suppression. Patients treated with CAELYX may require growth factors to support their blood counts.

Hepatic/Biliary/Pancreatic

The pharmacokinetics of CAELYX have not been studied in patients with hepatic impairment. Doxorubicin is known to be eliminated in large part by the liver. Thus CAELYX dosage should be reduced in patients with impaired hepatic function (see [4.2 Recommended Dose and Dosage Adjustment](#) and [10.3 Pharmacokinetics](#)). Prior to CAELYX administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin.

Diabetics

Precautions should be taken when using CAELYX in diabetics, since CAELYX is diluted in a (5%) Dextrose Injection USP solution.

Reproductive Health: Female and Male Potential

Women must avoid becoming pregnant and use contraception while receiving CAELYX and for up to eight months following discontinuation of CAELYX therapy (see [7.1.1 Pregnant Women](#)). Men must use contraception while receiving CAELYX and for up to six months following discontinuation of CAELYX therapy, so that their partner does not become pregnant.

- **Fertility**

No data exists on effects of the CAELYX on fertility.

- **Teratogenic Risk**

CAELYX can cause fetal harm when administered to pregnant women. CAELYX is embryotoxic in rat and embryotoxic and abortifacient in rabbits. Teratogenicity cannot be ruled out (see [2 Contraindications](#), and [7.1.1 Pregnant Women](#)).

Respiratory

Interstitial Lung Disease (ILD)

Interstitial lung disease (ILD), which may have an acute onset, has been observed in patients receiving CAELYX, including fatal cases (see 8 ADVERSE REACTIONS). If patients experience worsening of respiratory symptoms such as dyspnea, dry cough, and fever, Caelyx should be interrupted and the patient should be promptly investigated. If ILD is confirmed, Caelyx should be discontinued and the patient treated appropriately.

Skin

Palmar-Plantar Erythrodysesthesia (PPE)

In 254 breast cancer patients treated with CAELYX at a dose of 50 mg/m² body surface, every 4 weeks, 42 patients (17%) reported Grade III PPE, and no cases of Grade IV PPE were reported. Discontinuations due to PPE were infrequent (17 patients, 7%).

In 512 ovarian cancer patients treated with CAELYX at a dose of 50 mg/m² body surface, 100 patients (19.5%) reported Grade III treatment-related PPE and 3 patients (0.6%) reported Grade IV treatment-related PPE, with 19 patients (3.7%) discontinuing.

In 705 patients with AIDS-related Kaposi's sarcoma treated with CAELYX at 20 mg/m² body surface, 24 patients (3.4%) developed PPE with 3 patients (0.9%) discontinuing.

Palmar-plantar erythrodysesthesia is characterized by painful, macular reddening skin eruptions, swelling, and, for some patients, desquamation of the skin on the hands and the feet.

PPE was generally seen after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks with or without treatment with corticosteroids so that prolonged delay of therapy need not occur. However, dose modification may be required to manage PPE (see [4.2 Recommended Dose and Dosage Adjustment](#)). The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Strategies to prevent and treat PPE include keeping hands and feet cool by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight-fitting). PPE appears to be primarily related to the dose schedule and can be reduced by extending the CAELYX dose interval 1-2 weeks or reducing the CAELYX dose. In some settings, pyridoxine has been tried to ameliorate the symptoms of PPE.

Radiation Therapy

Skin recall reaction due to prior radiotherapy has occurred with CAELYX administration.

Second Primary Malignancies

Oral Neoplasms

Cases of secondary oral cancer (including fatalities) have been reported in patients exposed to CAELYX. Cases of secondary oral cancer were diagnosed both, during treatment with CAELYX, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer (see [8.5 Post-Market Adverse Reactions](#)).

Secondary Acute Myeloid Leukemia and Myelodysplastic Syndrome

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplastic syndrome have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with doxorubicin or CAELYX should be kept under hematologic supervision (see [8.5 Post-Market Adverse Reactions](#)).

7.1 Special Populations

7.1.1 Pregnant Women

CAELYX should not be administered to pregnant women. Women of childbearing potential must use effective contraceptive measures while they are receiving CAELYX and for up to eight months following discontinuation of CAELYX therapy.

CAELYX can cause fetal harm when administered to pregnant women. CAELYX is embryotoxic in rat and embryotoxic and abortifacient in rabbits. Teratogenicity cannot be ruled out (see [16 NON-CLINICAL TOXICOLOGY](#)).

7.1.2 Breast-feeding

There is no information regarding the presence of doxorubicin in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Precaution should be exercised because many drugs can be excreted in human milk. Due to the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should discontinue nursing prior to taking CAELYX.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>60 years of age): Experience with CAELYX in patients over 60 years of age is limited (see [10.3 Pharmacokinetics](#)).

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Breast Cancer

Breast Cancer Patients: 254 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with CAELYX at a dose of 50 mg/m² body surface, every 4 weeks in a phase III clinical trial. The most frequently reported treatment-related adverse effects included palmar-plantar erythrodysesthesia (PPE) (48.0%) and nausea

(37.0%) (Table 7). These effects were mostly mild and reversible, with severe (Grade III) cases reported in 17.0% and 3.0% respectively, and no reported incidences of life-threatening (Grade IV) cases for either PPE or nausea. Infrequently, these effects resulted in permanent treatment discontinuation (7.0% and 0% respectively). Pronounced alopecia (or total hair loss) was seen in only 7.0% of CAELYX-treated patients as compared with 54.0% of patients treated with doxorubicin.

Hematologic adverse effects were infrequently reported, were mostly mild or moderate in severity, and manageable. Anemia, neutropenia, leukopenia and thrombocytopenia were infrequently reported at incidences of 5.0%, 4.0%, 2.0%, and 1.0%, respectively. Life-threatening (Grade IV) hematologic effects were reported at incidences of <1.0%. The need for either growth factor support or transfusion support was minimal (5.1% and 5.5% of patients, respectively). Febrile neutropenia was reported in 3/254 (1.2%) patients treated with CAELYX and 8/255 (3.1%) patients treated with doxorubicin.

Table 7 Treatment-related Undesirable Effects Reported in ≥ 5% of CAELYX-treated Patients by Severity and Body System in Breast Cancer Clinical Trial (I97-328)

| AE body system | I97-328 All severities % | I97-328 Grades III/IV % |
|---------------------------------|--------------------------|-------------------------|
| Body as a Whole | | |
| Asthenia | 10 | 1 |
| Erythema | 7 | <1 |
| Fatigue | 12 | <1 |
| Fever | 8 | 0 |
| Weakness | 6 | <1 |
| Gastrointestinal | | |
| Abdominal Pain | 8 | 1 |
| Anorexia | 11 | 1 |
| Constipation | 8 | <1 |
| Diarrhea | 7 | 1 |
| Mouth Ulceration | 5 | <1 |
| Mucositis | 23 | 4 |
| Nausea | 37 | 3 |
| Stomatitis | 22 | 5 |
| Vomiting | 19 | <1 |
| Red Blood Cell Disorders | | |
| Anemia | 5 | 1 |
| Skin and Appendages | | |
| Alopecia | 20 | 0 |
| PPE* | 48 | 17 |
| Pigmentation abnormal | 8 | <1 |
| Rash | 10 | 2 |

* Palmar-plantar erythrodysesthesia (hand- foot syndrome). No cases of Grade IV (life-threatening) PPE were reported.

Ovarian Cancer

Ovarian Cancer Trials (Phase II and III)

Information on the adverse reactions is based on the experience in 512 patients with ovarian cancer treated at a dose of 50 mg/m² body surface. The median cumulative dose in the ovarian cancer trials was 150.6 mg/m², median cycle length was 30.0 days, and median days on drug was 65.5 days.

Of these 512 patients, a total of 509 patients (99.4%) in the ovarian cancer trials, reported a total of 5026 adverse events, and 484 (94.5%) patients reported treatment-related adverse events. Treatment-related fatal adverse events were reported in 4 (0.8%) patients, while Grade IV (life-threatening) treatment-related adverse events were reported by 38 (7.4%) patients.

Myelosuppression was mostly mild or moderate and manageable. Leukopenia (33.2%) was the most frequently reported hematological adverse event, followed by anemia (32.2%), neutropenia(31.6%) and thrombocytopenia (10.7%). Life-threatening (Grade IV) haematological effects were extremely rare (1.6%, 0.4%, 2.9% and 0.2%, respectively). Growth factor support was required infrequently (<5%) and transfusion support was required in approximately 15% of patients.

Frequently reported treatment-related adverse effects included palmar-plantar erythrodysesthesia(PPE) (46.1%) and stomatitis (38.9%). These effects were mainly mild, with severe (Grade III) cases reported in 19.5% and 8.0% respectively, and life-threatening (Grade IV) cases reported in 0.6% and 0.8% respectively. These resulted infrequently in permanent treatment discontinuation(<5% and <1% respectively).

Other frequently reported drug-related effects (≥5%) included nausea (38.1%), asthenia (34.0%),rash (25.0%), vomiting (24.4%), alopecia (17.4%), constipation (12.9%), anorexia (12.1%), mucous membrane disorder (14.5%), diarrhea (11.7%), abdominal pain (8.2%), fever (9.4%), paresthesia (7.6%), pain (7.4%), skin discoloration (6.1%), pharyngitis (6.4%), dry skin (5.9%), dyspepsia (5.5%) and somnolence (5.1%).

Table 8 Summary of Frequently Reported (≥1%) Treatment-related Adverse Events by Severity (Grade III/IV), Body System and COSTART Preferred Term Reported in Ovarian Cancer Patients

| Adverse Event | Ovarian Cancer Patients treated with CAELYX n=512 | | |
|--|--|----------|----------------|
| | n=484 (94.5%) | | |
| No. (%) of Patients Reporting Treatment-related Adverse Events | Grade III | Grade IV | All Severities |
| Body as a Whole | | | |
| Asthenia | 34 (6.6) | 0 | 174 (34.0) |
| Mucous Membrane Disorder | 16 (3.1) | 0 | 74 (14.5) |
| Digestive System | | | |

| | | | |
|-----------------------------------|---------------|----------|------------|
| Stomatitis | 41 (8.0) | 5 (0.8) | 199 (38.9) |
| Nausea | 21 (4.1) | 1 (0.2) | 195 (38.1) |
| Vomiting | 22 (4.3) | 3 (0.6) | 125 (24.4) |
| Hemic and Lymphatic System | | | |
| Leukopenia | 36 (7.0) | 8 (1.6) | 170 (33.2) |
| Anemia | 28 (5.5) | 2 (0.4) | 165 (32.2) |
| Neutropenia | 46 (9.0) | 15 (2.9) | 162 (31.6) |
| Thrombocytopenia | 6 (1.2) | 1 (0.2) | 55 (10.7) |
| Skin and Appendages | | | |
| Hand-Foot Syndrome* | 100 (19.5) | 3 (0.6) | 236 (46.1) |
| Rash | 17 (3.3) | 1 (0.2) | 128 (25.0) |
| Alopecia | 6 (1.2) | 0 | 89 (17.4) |

*Palmar-plantar erythrodysesthesia (PPE)

AIDS-KS

Information on adverse events is based on the experience reported in 711 patients with AIDS-KS enrolled in four open-label studies, as well as 254 patients enrolled in two controlled trials. The majority of patients were treated with 20 mg/m² (body surface) of CAELYX every two to three weeks.

Open-label trials

In the open-label trials, the median cumulative dose of CAELYX (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) was 120 mg/m² body surface. Overall, the immune status was poor in 90.1% of the patients enrolled in these studies, with a median CD4 count of 20 cells/mm³.

As expected, patients were receiving many concomitant medications. Over half (58.1%) of the patients were taking one of the four available antiretroviral medications; zidovudine (AZT) was the most frequently employed in 34.3% of patients, with didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) also used in decreasing order of frequency. Use and frequency of other antivirals was frequent: 55.7% received acyclovir at sometime during the trial, 28.9% received ganciclovir and 16.4% received foscarnet. Systemic antifungals were frequently employed with fluconazole being used by 75.7% of patients. Prophylactic therapy of opportunistic infections was used; sulfamethoxazole/trimethoprim being used the most, in 54.9% of patients.

In many instances, it was difficult to determine whether adverse events resulted from CAELYX, from concomitant therapy, or from the patients' underlying disease(s). Of the 711 patients for whom adverse events data are recorded, 84.6% reported one or more adverse events that were considered by the investigators to be possibly related, probably related or related to treatment with CAELYX. For patients who discontinued therapy, death was the most common reason (32.3% of patients). Adverse reactions only infrequently (5.3%) led to discontinuation of treatment.

Controlled trials

In the two controlled studies, the median dose of CAELYX administered per cycle was 20mg/m² body surface, and the mean duration of therapy with CAELYX was 81.1 days. The majority of patients were classified as poor risk. In all three groups, subcutaneous KS lesions were present in more than 98.4% of patients; 21.7% of patients had evidence of pulmonary KS; and 15.7% of patients had evidence gastrointestinal involvement. In all of the three groups, the majority of patients had CD4 cell counts of less than 50 cells/mm³.

Fewer CAELYX-treated patients died during the course of the controlled trials (16.9%). Early termination due to adverse events was observed in 10.6% of CAELYX-treated patients. In general, the safety profile of the patients treated in the controlled studies was consistent with the safety profile of the patients that were treated with CAELYX in the open-label trials. Opportunistic infections, such as candidiasis (47.8%), cytomegalovirus (37.5%), *Pneumocystis carinii* pneumonia (20.6%), and *Mycobacterium avium* complex (10.1%), regardless of causality, have been frequently observed in patients with AIDS-KS receiving CAELYX. The table below shows all events occurring at ≥5% in the open-label and controlled trials, that were considered by investigators, at least possibly related to the study drug.

Table 9 Possibly or Probably Drug-Related Adverse Events by Body System and Costart Preferred Term Including Open Label Studies - Reported in ≥5% of AIDS-KS Patients.

| | CAELYX (Open Label) ¹ | CAELYX (Comparator) ² | ABV ³ | BV ⁴ |
|---|-------------------------------------|-------------------------------------|-------------------|-------------------|
| Number of Patients | 711 | 254 | 125 | 1 2 0 |
| Number of Patients Reporting Adverse Events | 566 (79.6%) | 192 (75.6%) | 114 (91.2%) | 92 (76.7%) |
| Number of Patients by Body System and Preferred COSTART Term Incidence | | | | |
| Body as a whole | 165 (23.2%) | 55 (21.7%) | 72 (57.6%) | 43 (35.8%) |
| asthenia | 67 (9.4%) | 29 (11.4%) | 37 (29.6%) | 10 (8.3%) |
| fever | 62 (8.7%) | 13 (5.1%) | 38 (30.4%) | 22 (18.3%) |
| headache | 30 (4.2%) | 7 (2.8%) | 9 (7.2%) | 4 (3.3%) |
| abdominal pain | 16 (2.3%) | 3 (1.2%) | 7 (5.6%) | 1 (0.8%) |
| chills | 8 (1.1%) | 2 (0.8%) | 8 (6.4%) | 6 (5.0%) |
| pain | 10 (1.4%) | 3 (1.2%) | 7 (5.6%) | 2 (1.7%) |
| lab test abnormal | 3 (0.4%) | 8 (3.1%) | 0 | 7 (5.8%) |
| chills and fever | 2 (0.3%) | 2 (0.8%) | 6 (4.8%) | 6 (5.0%) |
| malaise | 3 (0.4%) | 2 (0.8%) | 6 (4.8%) | 1 (0.8%) |
| Cardiovascular system | 2 (0.3%) | 1 (0.4%) | 6 (4.8%) | 1 (0.8%) |
| phlebitis | 2 (0.3%) | 1 (0.4%) | 6 (4.8%) | 1 (0.8%) |
| Digestive system | 207 (29.1%) | 57 (22.4%) | 77 (61.6%) | 37 (30.8%) |
| nausea | 91 (12.8%) | 36 (14.2%) | 54 (43.2%) | 14 (11.7%) |
| diarrhea | 53 (7.5%) | 10 (3.9%) | 11 (8.8%) | 3 (2.5%) |
| stomatitis | 45 (6.3%) | 12 (4.7%) | 4 (3.2%) | 2 (1.7%) |
| nausea and vomiting | 29 (4.1%) | 2 (0.8%) | 15 (12.0%) | 10 (8.3%) |
| vomiting | 25 (3.5%) | 8 (3.1%) | 17 (13.6%) | 3 (2.5%) |
| oral moniliasis | 40 (5.6%) | 2 (0.8%) | 2 (1.6%) | 4 (3.3%) |

| | | | | |
|-----------------------------------|--------------------|--------------------|-------------------|-------------------|
| anorexia | 8 (1.1%) | 6 (2.4%) | 17 (13.6%) | 3 (2.5%) |
| constipation | 12 (1.7%) | 2 (0.8%) | 8 (6.4%) | 9 (7.5%) |
| Hemic and lymphatic system | 471 (66.2%) | 144 (56.7%) | 63 (50.4%) | 49 (40.8%) |
| leukopenia | 435 (61.2%) | 138 (54.3%) | 56 (44.8%) | 46 (38.3%) |
| anemia | 145 (20.4%) | 19 (7.5%) | 14 (11.2%) | 9 (7.5%) |
| thrombocytopenia | 66 (9.3%) | 15 (5.9%) | 6 (4.8%) | 12 (10.0%) |
| hypochromic anemia | 68 (9.6%) | 9 (3.5%) | 6 (4.8%) | 6 (5.0%) |
| Nervous system | 15 (2.1%) | 10 (3.9%) | 30 (24.0%) | 28 (23.3%) |
| paresthesia | 6 (0.8%) | 6 (2.4%) | 14 (11.2%) | 14 (11.7%) |
| neuropathy | 4 (0.6%) | 3 (1.2%) | 9 (7.2%) | 11 (9.2%) |
| peripheral neuritis | 6 (0.8%) | 2 (0.8%) | 10 (8.0%) | 5 (4.2%) |
| Skin and appendages | 81 (11.4%) | 30 (11.8%) | 55 (44.0%) | 12 (10.0%) |
| alopecia | 63 (8.9%) | 18 (7.1%) | 53 (42.4%) | 10 (8.3%) |
| rash | 19 (2.7%) | 12 (4.7%) | 5 (4.0%) | 2 (1.7%) |

1. Patients treated with CAELYX in the open-label studies.
2. Patients treated with CAELYX in the controlled studies (vs. ABV or BV).
3. ABV (adriamycin, bleomycin, vincristine)
4. BV (bleomycin, vincristine)

8.3 Less Common Clinical Trial Adverse Reactions

Breast Cancer

Undesirable effects reported between $\geq 1\%$ and $< 5\%$ in 254 CAELYX-treated breast cancer patients, not previously reported in CAELYX clinical trials were breast pain, leg cramps, edema, leg edema, peripheral neuropathy, oral pain, ventricular arrhythmia, folliculitis, bone pain, musculo-skeletal pain, thrombocytopenia, cold sores (non-herpetic), fungal infection, epistaxis, upper respiratory tract infection, bullous eruption, dermatitis, erythematous rash, dry skin, pruritus, skin discoloration, scaly skin, nail disorder, lacrimation, blurred vision, flushing, weight decrease, dyspepsia and dyspnea.

Ovarian Cancer

Less frequently (1 to $< 5\%$) reported undesirable effects included peripheral edema, oral moniliasis, vasodilatation, mouth ulceration, pruritus, allergic reaction, dehydration, dyspnea, vesiculobullous rash, chills, infection, weight loss, esophagitis, skin disorder, exfoliative dermatitis, cardiovascular disorder, chest pain, dizziness, maculopapular rash, gastritis, myalgia, back pain, depression, insomnia, dysphagia, increased cough, sweating, nausea and vomiting, malaise, taste perversion, urinary tract infection, conjunctivitis, acne, gingivitis, herpes zoster, hypochromic anemia, anxiety, vaginitis, headache, flatulence, dry mouth, cachexia, neuropathy, hypertonia, skin ulcer and dysuria.

AIDS-KS

Incidence 1% to 5% (Possibly or Probably Related) in CAELYX-Treated AIDS-KA Patients

Body as a Whole: allergic reaction, anaphylactoid reaction, back pain, chest pain, flu syndrome, infection, mucous membrane disorder, pain.

Cardiovascular: hypotension, tachycardia, vasodilatation.

Digestive System: aphthous stomatitis, dyspepsia, dysphagia, glossitis, liver function tests abnormal, mouth ulceration.

Hemic and Lymphatic System: hemolysis, pancytopenia, prothrombin increased.

Metabolic/Nutritional: bilirubinemia, SGOT increased, SGPT increased, weight loss.

Nervous System: dizziness, emotional lability, somnolence.

Respiratory System: dyspnea, pneumonia.

Skin and Appendages: dry skin, herpes simplex, pruritus.

Others: retinitis, albuminuria.

Incidence Less than 1% (Possibly or Probably Related) in CAELYX-Treated AIDS-KA Patients

Body As A Whole: abscess, cellulitis, substernal chest pain, cryptococcosis, facial edema, hypothermia, immune system disorder, injection site hemorrhage, injection site pain, injectionsite reaction, moniliasis, neoplasm, radiation injury, sepsis.

Cardiovascular System: arrhythmia, bradycardia, bundle branch block, cardiomegaly, cardiovascular disorder, congestive heart failure, deep thrombophlebitis, heart failure, hemorrhage, migraine, palpitation, pericardial effusion, peripheral vascular disorder, supraventricular extrasystoles, syncope, thrombophlebitis, thrombosis, ventricular arrhythmia, ventricular extrasystoles.

Digestive System: bloody diarrhea, cholestatic jaundice, colitis, dry mouth, eructation, esophageal ulcer, esophagitis, fecal impaction, gastritis, GI hemorrhage, gingivitis, hematemesis, hepatic failure, hepatitis, hepatosplenomegaly, increased appetite, jaundice, leukoplakia of mouth, liver damage, melena, pancreatitis, rectal disorder, sclerosing cholangitis, tenesmus, ulcerative proctitis, ulcerative stomatitis.

Endocrine System: diabetes mellitus.

Hemic and Lymphatic System: eosinophilia, erythrocytes abnormal, lymphadenopathy, lymphangitis, lymphedema, lymphoma-like reaction, marrow depression, petechia, purpura, thromboplastin decreased.

Metabolic/Nutritional: BUN increased, cachexia, creatinine increased, dehydration, edema, hypercalcemia, hyperkalemia, hyperlipemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, ketosis, LDH increased, peripheral edema, weight gain.

Musculoskeletal System: arthralgia, bone disorder, bone pain, joint disorder, myalgia, myasthenia, myositis.

Nervous System: abnormal dreams, abnormal gait, acute brain syndrome, anxiety, cerebrovascular accident, confusion, convulsion, depression, dysarthria, dyskinesia,

hypertonia, hypokinesia, hypotonia, insomnia, nervousness, nystagmus, paralysis, reflexes decreased, thinking abnormal, vertigo.

Respiratory System: asthma, bronchitis, cough increased, hiccup, hyperventilation, lung disorder, pharyngitis, pleural effusion, pneumothorax, rhinitis, sinusitis.

Skin and Appendages: acne, cutaneous moniliasis, eczema, erythema nodosum, exfoliative dermatitis, furunculosis, herpes zoster, leukoderma, maculopapular rash, psoriasis, pustular rash, seborrhea, skin discoloration, skin necrosis, skin ulcer.

Special Senses: abnormal vision, blindness, conjunctivitis, diplopia, eye disorder, eye pain, optic neuritis, otitis media, taste perversion, tinnitus.

Urogenital System: balanitis, cystitis, dysuria, genital edema, glycosuria, hematuria, kidney failure, kidney function abnormal, prostatic disorder, testis disorder, urine abnormality.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Breast Cancer

Clinically significant laboratory abnormalities (Grades III and IV) in this breast cancer group included increases in total bilirubin (2.4%) and AST (1.6%).

Increases in ALT were less frequent (<1%). No clinically significant increases in serum creatinine were reported. Clinically significant hematologic measurements were infrequent and low as measured by leukopenia (4.3%), anemia (3.9%), neutropenia (1.6%) and thrombocytopenia (1.2%). Sepsis was reported at an incidence of 1%. See Table 7.

Ovarian Cancer

In the subset of patients with ovarian cancer, clinically significant laboratory abnormalities occurring in clinical trials with CAELYX included increases in total bilirubin (usually in patients with liver metastases) (5%) and serum creatinine levels (5%).

Clinically significant measurements, measured by Grades III and IV neutropenia (11.4%), anemia (5.7%), and thrombocytopenia (1.2%) were low. Increases in AST were less frequently (<1%) reported. Sepsis related to leukopenia was observed infrequently (<1%).

Pivotal Phase III Trial - Ovarian Cancer

In the pivotal phase III ovarian cancer trial, the toxicity profiles of the two agents, CAELYX and topotecan were very different.

Hematologic toxicity was more frequent and usually Grade III, IV in the topotecan-treated patients in comparison with CAELYX (neutropenia 77% vs 12%, thrombocytopenia 34% vs 1%, and anemia 28% vs 5% respectively). Grade III, IV hematologic adverse events were observed in 90% of topotecan-treated patients compared with 55% of CAELYX-treated patients.

Most drug-related adverse events associated with CAELYX were mild to moderate in severity with the exceptions of palmar-plantar erythrodysesthesia (PPE) and stomatitis. However, PPE and stomatitis were managed successfully with dose modifications and rarely resulted in study discontinuation (4% for PPE and 1% for stomatitis).

There was no evidence of a relationship between cumulative CAELYX dose and change from baseline for LVEF (left ventricular ejection fraction).

Topotecan-associated toxicities more often resulted in morbidity and life-threatening sequelae than the primary CAELYX-related adverse events.

In the pivotal phase III ovarian cancer study, comparing CAELYX vs. topotecan, three deaths in the topotecan group due to neutropenic sepsis were considered treatment-related. There were no treatment-related deaths in the CAELYX group. There were no cases of treatment-related sepsis or neutropenic fever in the CAELYX group.

Table 10 Treatment-Related Adverse Events Reported by >10% of Patients in Either Ovarian Cancer Treatment Group (Pivotal Phase III Study)

| Any Adverse Event | CAELYX (n=239) | | | Topoteca n(n=235) | | |
|---|-------------------|--------------|---------|----------------------|-----------|--------------|
| | All | Grade III | Grade | All | Grade III | Grade IV |
| | 222 (93%) | 132 (55%) | 20 (8%) | 232 (99%) | 176 (75%) | 158 (67%) |
| Body as a whole | | | | | | |
| Asthenia | 75 (31%) | 13 (5%) | 0 | 104 (44%) | 17 (7%) | 0 |
| Mucous membrane disorder | 33 (14%) | 8 (3%) | 0 | 7 (3%) | 0 | 0 |
| Fever | 28 (12%) | 0 | 0 | 49 (21%) | 6 (3%) | 5 (2%) |
| Abdominal pain | 20 (8%) | 3 (1%) | 0 | 29 (12%) | 3 (1%) | 1 (<1%) |
| Digestive System | | | | | | |
| Stomatitis | 95 (40%) | 19 (8%) | 1 (<1%) | 35 (15%) | 1 (<1%) | 0 |
| Nausea | 85 (36%) | 6 (3%) | 1 (<1%) | 127 (54%) | 12 (5%) | 2 (1%) |
| Vomiting | 58 (24%) | 11 (5%) | 2 (1%) | 81 (35%) | 14 (6%) | 2 (1%) |
| Constipation | 33 (14%) | 0 | 0 | 58 (25%) | 3 (1%) | 1 (<1%) |
| Diarrhea | 28 (12%) | 4 (2%) | 0 | 49 (21%) | 5 (2%) | 1 (<1%) |
| Anorexia | 26 (11%) | 1 (<1%) | 0 | 32 (14%) | 1 (<1%) | 0 |
| Hematopoietic and Lymphatic System | | | | | | |
| Leukopenia | 87 (36%) | 21 (9%) | 3 (1%) | 149 (63%) | 82 (35%) | 35 (15%) |
| Anemia | 85 (36%) | 12 (5%) | 1 (<1%) | 169 (72%) | 58 (25%) | 8 (3%) |
| Neutropenia | 84 (35%) | 19 (8%) | 10 (4%) | 191 | 33 (14%) | 145 |

| | | | | | | |
|----------------------------|-----------|----------|--------|--------------|----------|----------|
| | | | | (81%) | | (62%) |
| Thrombocytopenia | 31 (13%) | 3 (1%) | 0 | 152 (65%) | 40 (17%) | 40 (17%) |
| Skin and Appendages | | | | | | |
| PPE* | 117 (49%) | 53 (22%) | 2 (1%) | 2 (1%) | 0 | 0 |
| Rash | 58 (24%) | 10 (4%) | 0 | 18 (8%) | 1 (<1%) | 0 |
| Alopecia | 38 (16%) | 3 (1%) | 0 | 115 (49%) | 14 (6%) | 0 |

* Palmar-plantar erythrodysesthesia

8.5 Post-Market Adverse Reactions

The following serious adverse reactions have been derived from spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System: myelosuppression associated with anemia, thrombocytopenia, leukopenia, febrile neutropenia.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): secondary oral cancer including fatal cases (see [7 WARNINGS AND PRECAUTIONS, Second Primary Malignancies, Oral Neoplasms](#)), secondary acute myeloid leukemia and myelodysplastic syndrome (see [7 WARNINGS AND PRECAUTIONS, Secondary Acute Myeloid Leukemia and Myelodysplastic Syndrome](#)).

Nervous System: convulsions (see [7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions](#)).

Skin and Subcutaneous Tissue: serious skin conditions including erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, lichenoid keratosis.

Vascular: thrombophlebitis, venous thrombosis, pulmonary embolism. Patients with cancer are at increased risk for thromboembolic disease.

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with CAELYX. CAELYX may interact with drugs known to interact with the conventional formulation of doxorubicin hydrochloride.

In patients who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.

9.3 Drug-Behavioural interactions

Drug behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

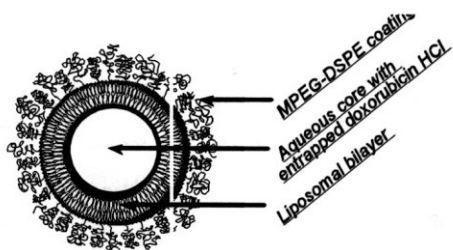
10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The active ingredient of CAELYX (Pegylated Liposomal Doxorubicin Hydrochloride for Injection) is doxorubicin hydrochloride. The mechanism of action of doxorubicin hydrochloride is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

CAELYX is doxorubicin hydrochloride encapsulated in long-circulating STEALTH[®] liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH[®] liposomes of CAELYX are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Representation of a STEALTH[®] liposome:



STEALTH[®] liposomes have a half-life of approximately 73.9 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug

(the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated CAELYX liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH® liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH® liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors. Once the STEALTH® liposomes distribute to the tissue compartment, the encapsulated doxorubicin hydrochloride becomes available. The exact mechanism of release is not understood.

10.3 Pharmacokinetics

The pharmacokinetics of CAELYX was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of CAELYX over the dose range of 10 mg/m² to 60 mg/m² body surface, was best described by a two-compartment non-linear model with zero-order input and Michaelis-Menten elimination. The mean intrinsic clearance of CAELYX was 0.030 L/h/m² (range 0.008 to 0.152 L/h/m²) and the mean central volume of distribution was 1.93 L/m² (range 0.96 - 3.85 L/m²) approximating the plasma volume. The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours. The apparent non-linearity suggests that the clearance of CAELYX is saturable, and that greater than dose-proportional increases in exposure occur as the dose is increased.

Breast Cancer

The pharmacokinetics of CAELYX determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.0160 L/h/m² (range 0.0080 - 0.027 L/h/m²), the mean central volume of distribution was 1.46 L/m² (range 1.10 - 1.64 L/m²). The mean apparent half-life was 71.5 hours (range 45.2 - 98.5 hours).

Ovarian Cancer

The pharmacokinetics of CAELYX determined in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.021 L/h/m² (range 0.009 – 0.041 L/h/m²), the mean central volume of distribution was 1.95 L/m² (range 1.67 – 2.40 L/m²). The mean apparent half-life was 75.0 hours (range 36.1 – 125 hours).

AIDS-KS

The plasma pharmacokinetics, and tumor localization of CAELYX were studied in 42 patients with AIDS- related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m² body surface, administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m² body surface, with a 3-week wash-out period between doses. The pharmacokinetic parameter values of CAELYX are presented in the following table:

Table 11 - Pharmacokinetic Parameters in CAELYX-Treated Patients(Mean ± SD)

| Parameter (units) | Dose | |
|---|---|---|
| | 10 mg/m ² bodysurface (n=23) | 20 mg/m ² bodysurface (n=23) |
| Peak Plasma Concentration (mcg/mL) | 4.12 ± 0.215 | 8.34 ± 0.49 |
| Plasma Clearance (L/h/m ²) | 0.0556 ± 0.01 | 0.041 ± 0.004 |
| Steady-State Volume of Distribution(L/m ²) | 2.83 ± 0.145 | 2.72 ± 0.120 |
| AUC (mcg/mL•h) | 277 ± 32.9 | 590 ± 58.7 |
| First Phase (λ_1) Half-Life (h) | 4.7 ± 1.1 | 5.2 ± 1.4 |
| Second Phase (λ_2) Half-Life (h) | 52.3 ± 5.6 | 55.0 ± 4.8 |

Across this dosage range, CAELYX displayed linear pharmacokinetics. Disposition occurred in two phases after CAELYX administration, with a relatively short first phase (~5 hours) and a prolonged second phase (~55 hours) that accounted for the majority of the area under the curve (AUC).

In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, the steady-state volume of distribution of CAELYX indicated that CAELYX was confined mostly to the vascular fluid volume. Plasma protein binding of CAELYX has not been determined; however, the plasma protein binding of doxorubicin is approximately 70%.

Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range: 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m² (body surface) of CAELYX. The plasma clearance of CAELYX was slow, with a mean clearance value of 0.042 L/h/m² at a dose of 20 mg/m² body surface.

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours post infusion of 10 or 20 mg/m² (body surface) of CAELYX in 22 patients. Significantly higher doxorubicin concentrations were found in KS lesions than in normal skin biopsies at both sampling times and dose levels. The median doxorubicin concentrations ranged from 2-fold to 20-fold higher in KS lesions than in normal skin.

Distribution:

The concentration of CAELYX in AIDS-KS lesions was a median of 21 times higher than in normal skin at 48 hours post-treatment. Population pharmacokinetic analyses suggested that there were small differences in the volume of distribution between tumor types, with the largest volume of distribution in patients with AIDS-KS (2.24 L/m²), and the smallest volume of distribution in patients with breast carcinoma (1.12 L/m²). The volume of distribution in the ovarian carcinoma population is 1.56 L/m².

Special Populations and Conditions

- **Geriatrics:** The population-based pharmacokinetic analysis included patients from 21 to 73 years of age. The results of this analysis suggested that age did not influence the

pharmacokinetic profile of CAELYX.

- **Hepatic Insufficiency:** Based upon population pharmacokinetics, bilirubin concentrations did not affect the pharmacokinetics of CAELYX. It should be noted however, that few patients with elevated bilirubin were included in the analysis and that the highest bilirubin in the study was 4.0 mg/dL. Until more data are available demonstrating the safety of CAELYX in this patient population, suggested dosing reductions mentioned under [4 DOSAGE AND ADMINISTRATION](#) should be followed.
- **Renal Insufficiency:** As doxorubicin is metabolized by the liver and excreted in the bile, dose modification should not be required with CAELYX. Population-based analysis confirms that changes in renal function over the range tested (estimated creatinine clearance 30-156 mL/min) do not alter the pharmacokinetics of CAELYX. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 mL/min.

11 STORAGE, STABILITY AND DISPOSAL

- CAELYX should not be used after the expiry date stated on the label and carton.
- Unopened vials of CAELYX should be stored at 2 °C to 8 °C. Avoid freezing.
- After dilution:
 - Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C.
 - From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C.
 - Partially used vials should be discarded. CAELYX should be handled and disposed of in a manner consistent with that of other anti-cancer drugs.

12 SPECIAL HANDLING INSTRUCTIONS

Caution should be exercised in handling CAELYX dispersion. The use of gloves is required. If CAELYX comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water.

- CAELYX should not be used if it shows evidence of precipitation or any other particulate matter.
- CAELYX should not be used if it shows a discoloration of the dispersion.
- Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

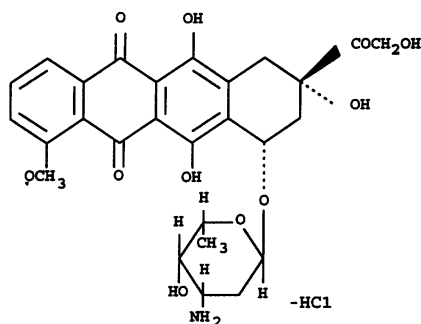
Drug Substance

Proper name: Doxorubicin Hydrochloride

Chemical name: (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy] -8- glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12- naphthacenedione hydrochloride

Molecular formula and molecular mass: C₂₇ H₂₉ NO₁₁•HCl and 579.99

Structural formula:



Physicochemical properties: Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*. It is a red- orange, odorless, crystalline powder, m.p. 204°C - 205°C, pH (conc. 5 mg/mL) 4.0 - 5.5, pKa 8.22, $[\alpha]^{20}_D$ +268°- 270° (conc. 0.1% methanol), soluble in water and alcohols.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Breast Cancer

A phase III randomized, controlled parallel-group, open-label, multicentre study of CAELYX 50 mg/m² q 4 weeks vs, doxorubicin hydrochloride 60 mg/m² q 3 weeks in patients with metastatic breast cancer was completed in 509 patients.

The protocol-specified primary objective of demonstrating non-inferiority between CAELYX and doxorubicin was met, the hazard ratio (HR) for progression-free survival (PFS) was 1.00 (95% CI for HR= 0.82 - 1.22). The treatment HR for PFS when adjusted for prognostic variables was consistent with PFS for the ITT population. Median PFS for CAELYX was 6.9 months and for doxorubicin 7.8 months, not statistically significant.

Table 12 - Progression-Free Survival in Breast Cancer Patients

| Protocol No. I97-328 | | | | | | | |
|----------------------|-----|--------------------|-------------------------|------------|----------------------|------|----------------------------|
| | n | Number of Subjects | | Median PFS | P-value ^b | HR | 95% CI for HR ^c |
| | | Censored | Progressed ^a | | | | |
| CAELYX | 254 | 52 | 202 | 6.9 months | 0.99 | 1.00 | 0.82-1.22 |
| Doxorubicin | 255 | 47 | 208 | 7.8 months | | | |

a: Deaths within 4 months of last tumor evaluation indicating no progression are considered events. b: Stratified log rank test to test superiority of CAELYX to doxorubicin. c: Adjusted for the interim analysis (95.01% CI provided).

Figure #1: Kaplan-Meier Curve for Progression-free Survival in Breast Cancer Patients

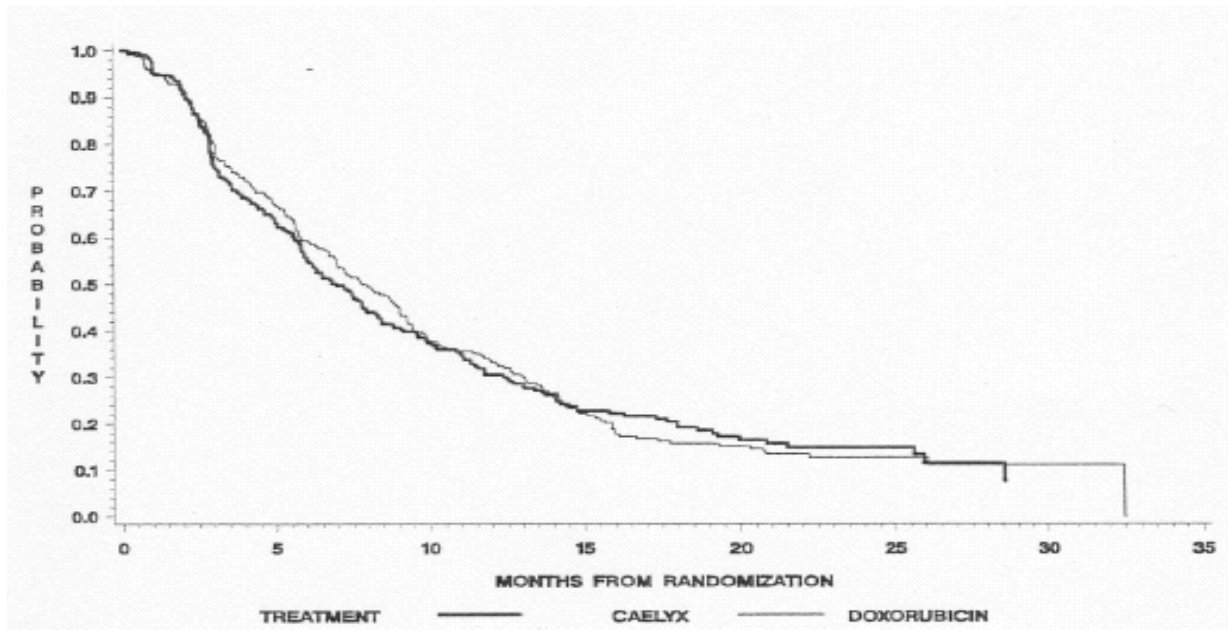


Table 13 - Overall Survival in Breast Cancer Patients

| | n | Censored | Dead | Media nOS | P-value ^a | HR | 95% CI forHR ^b |
|-------------|-----|----------|------|-----------|----------------------|-----|---------------------------|
| CAELYX | 254 | 110 | 144 | 21 months | 0.59 | 0.9 | 0.74-1.19 |
| Doxorubicin | 255 | 113 | 142 | 22 months | | | |

a: Stratified log rank test to test superiority of CAELYX to doxorubicin
b: Adjusted for the interim analysis (95.01% CI provided)

Figure #2: Kaplan-Meier Curve for Overall Survival in Breast Cancer Patient

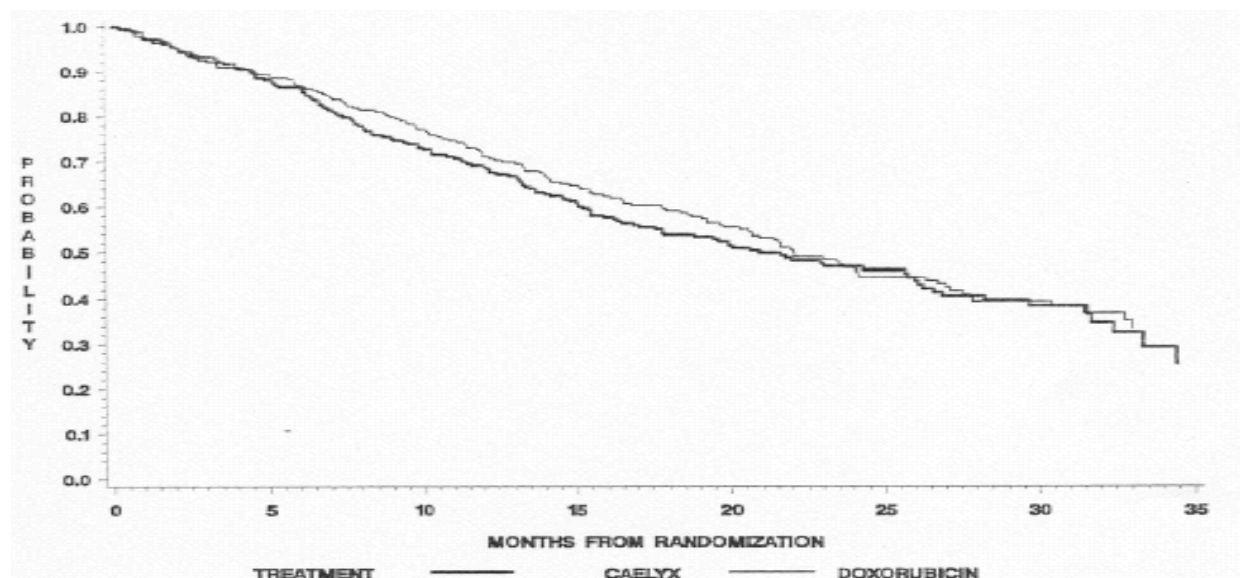


Table 14 - Objective Response to Treatment in Breast Cancer Patients

| | Number (%) of Subjects ^a | |
|---------------------------|-------------------------------------|---------------------|
| | CAELYX (n=209) | Doxorubicin (n=201) |
| Overall Response (CR+ PR) | 68 (33) | 77 (38) |
| Complete Response (CR) | 7 (3) | 9 (4) |
| Partial Response (PR) | 61 (29) | 68 (34) |
| Stable Disease (SD) | 52 (25) | 51 (25) |
| Progressive Disease (PD) | 37 (18) | 22 (11) |
| No assessment | 52 (25) | 51 (25) |

a: Based on the number of subjects with measurable disease.

In the breast cancer pivotal phase III trial comparing CAELYX (50 mg/m² every 4 weeks) to doxorubicin (60 mg/m² every 3 weeks), 10/254 patients randomized to receive CAELYX versus 48/255 patients randomized to receive doxorubicin met the protocol-defined criteria for cardiotoxicity during treatment and/or follow-up. Cardiotoxicity was defined as a decrease of 20 percentage points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 percentage points or greater if the LVEF became abnormal (less than the lower limit for normal). The risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with CAELYX than with doxorubicin (HR [doxorubicin/CAELYX] = 3.16, *P*<0.001). At cumulative doses greater than 450 mg/m² there were no cardiac events with CAELYX. Patients were also assessed for signs and symptoms of congestive heart failure (CHF). None of the 10 CAELYX patients, who had cardiotoxicity by LVEF

criteria, developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin patients, who had cardiotoxicity by LVEF criteria, developed signs and symptoms of CHF.

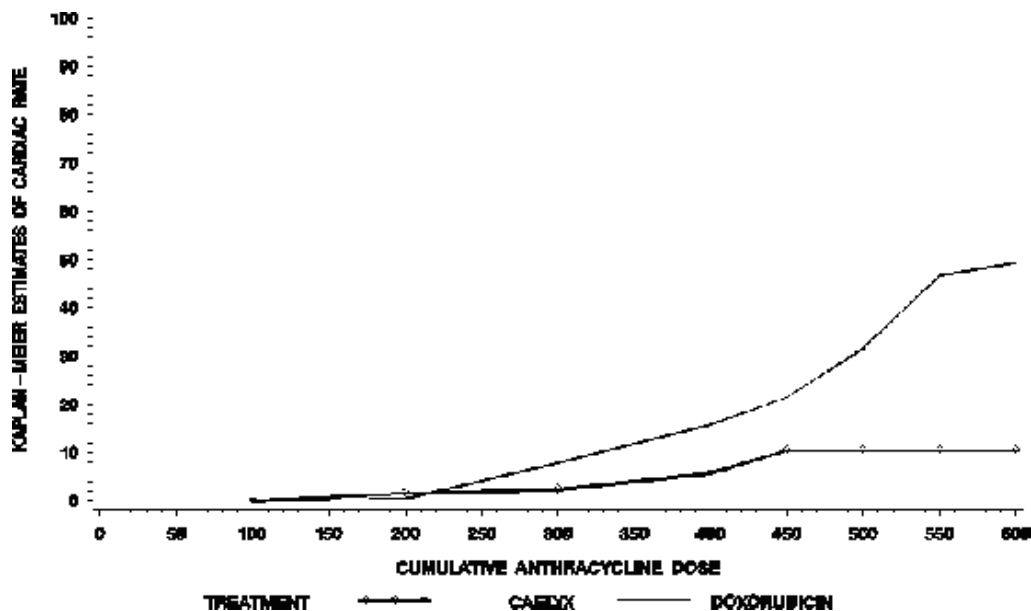
Table 15 - Cardiac Toxicity During Treatment and Follow-Up in Breast Cancer Patients

| Protocol No. I97-328 | | |
|--|--------------------|------------------------|
| | Number of Subjects | |
| | CAELYX (n=254) | Doxorubicin (n=255) |
| Subjects developed cardiotoxicity (LVEF defined) | 10 | 48 |
| Cardiotoxicity (with signs & symptoms of CHF) | 0 | 10 |
| Cardiotoxicity (no signs & symptoms of CHF) | 10 | 38 |

Table 16 - Cumulative Anthracycline Dose and Cardiotoxicity in Breast Cancer Patients Subgroups

| | Number of Subjects | | | | |
|------------------------------|--------------------|----------|-----------------------|------|---------------|
| | n | Censored | Cardiotoxicity Events | HR | 95% CI for HR |
| ≥55 years old | 159 | 153 | 6 | 2.04 | 0.81-5.18 |
| CAELYX | 152 | 134 | 18 | | |
| Doxorubicin | | | | | |
| Prior Adjuvant Anthracycline | 38 | 37 | 1 | 7.27 | 0.93-56.80 |
| CAELYX | 40 | 29 | 11 | | |
| Doxorubicin | | | | | |
| Cardiac Risk Factor | 122 | 117 | 5 | 2.7 | 1.01-7.18 |
| CAELYX | 121 | 100 | 21 | | |
| Doxorubicin | | | | | |

Figure #3: Kaplan-Meier Curve for Rate of Cardiotoxicity vs. Cumulative Anthracycline Dose in Breast Cancer Patients



In 418 patients with solid tumors (including a subset of patients with breast and ovarian cancers) treated with CAELYX at a dose of 50 mg/m²/cycle, the incidence of clinically significant cardiac dysfunction was low. Only 13 of 88 patients (15%) with cumulative anthracycline dose >400 mg/m² body surface, had a clinically significant change in their LVEF (defined as LVEF <45% or a decrease of at least 20 percentage points from baseline).

In addition, endomyocardial biopsies were performed in 8 solid tumor patients with cumulative anthracycline dose of 509 mg/m²-1,680 mg/m² body surface. The range of Billingham cardiotoxicity scores was grades 0-1.5. These grading scores are consistent with no or mild cardiotoxicity.

Table 17 - Most Common Treatment Related (≥5%) Adverse Events in Breast Cancer Patients

| | Number (%) of Subjects | | | | | |
|-----------|------------------------|---------|---------|------------------------|---------|---------|
| | CAELYX (n=254) | | | Doxorubicin (n=255) | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| PPE | 123 (48) | 42 (17) | 0 | 5 (2) | 0 | 0 |
| Nausea | 94 (37) | 8 (3) | 0 | 136 (53) | 12 (5) | 0 |
| Mucositis | 59 (23) | 10 (4) | 0 | 33 (13) | 5 (2) | 0 |

| | | | | | | |
|--------------------------|---------|--------|--------|----------|--------|--------|
| Stomatitis | 55 (22) | 12 (5) | 0 | 38 (15) | 4 (2) | 0 |
| Alopecia | 51 (20) | 0 | 0 | 169 (66) | 0 | 0 |
| Vomiting | 48 (19) | 2 (<1) | 0 | 78 (31) | 11 (4) | 0 |
| Fatigue | 31 (12) | 2 (<1) | 0 | 40 (16) | 4 (2) | 0 |
| Anorexia | 27 (11) | 3 (1) | 0 | 26 (10) | 1(<1) | 0 |
| Asthenia | 26 (10) | 3 (1) | 0 | 32 (13) | 3 (1) | 0 |
| Rash | 25 (10) | 6 (2) | 0 | 4 (2) | 0 | 0 |
| Abdominal Pain | 21 (8) | 3 (1) | 0 | 11 (4) | 3 (1) | 0 |
| Constipation | 21 (8) | 2 (<1) | 0 | 24 (9) | 1 (<1) | 0 |
| Pigmentation Abnormal | 21 (8) | 1 (<1) | 0 | 6 (2) | 1 (<1) | 0 |
| Fever | 20 (8) | 0 | 0 | 18 (7) | 2 (<1) | 1 (<1) |
| Diarrhea | 18 (7) | 3 (1) | 0 | 20 (8) | 2 (<1) | 0 |
| Erythema | 18 (7) | 2 (<1) | 0 | 3 (1) | 0 | 0 |
| Weakness | 14 (6) | 1 (<1) | 0 | 20 (8) | 4 (2) | 0 |
| Mouth Ulceration | 13 (5) | 1 (<1) | 0 | 9 (4) | 0 | 0 |
| Anemia | 12 (5) | 2 (<1) | 1(<1) | 19 (7) | 3 (1) | 1(<1) |
| Neutropenia | 10 (4) | 3(1) | 1 (<1) | 25 (10) | 10 (4) | 9 (4) |

Ovarian Cancer

Pivotal Phase III Study

A phase III comparative study of CAELYX versus topotecan in patients with epithelial ovarian cancer following failure of first-line, platinum-based chemotherapy was completed in 474 patients. All patients entered into this study had failed a first-line platinum-containing regimen, usually a combination of platinum and paclitaxel, either used in combination or in sequence. A small number of patients had received prior therapy with platinum alone.

Pivotal Phase III Study-Efficacy

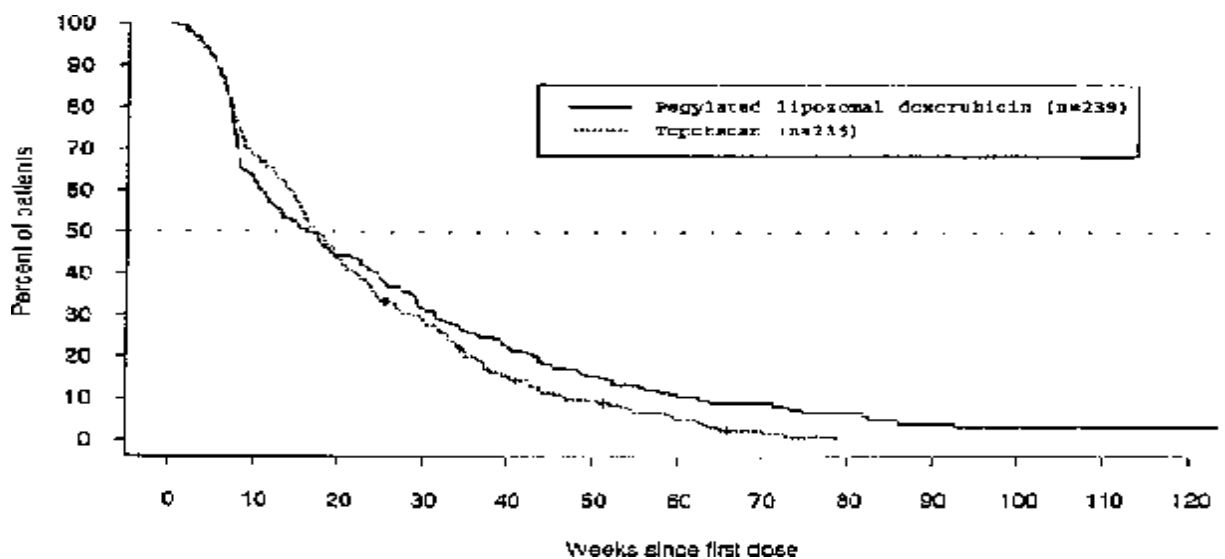
For the protocol-specified primary endpoint of time to progression for the 416 (207 CAELYX, 209 topotecan) evaluable patients (patients who were randomized, met enrolment criteria, and received at least 2 cycles of study drug), the results of the study demonstrate therapeutic equivalency of CAELYX vs. topotecan. The median time to progression for evaluable patients was 148 days for CAELYX and 134 days for topotecan with a hazard ratio of 1.262, 90% CI 1.062-1.500, $P=0.026$.

The time to progression for the Intent to Treat (ITT) population $n=474$ (239 CAELYX, 235 topotecan; patients who were randomized and received at least a partial dose of study drug) favored CAELYX over topotecan with a hazard ratio of 1.176, 90% CI 1.002-1.381, $P=0.095$. The median time to progression was 113 days for CAELYX and 119 days for topotecan.

Table 18 - Objective Response, Overall Response and Stratified by Platinum Sensitivity (ITT Ovarian Cancer Population)

| | CAELYX (n=239) | Topotecan (n=235) |
|---------------------|----------------|-------------------|
| Overall Response | | |
| n | 239 | 235 |
| Total | 47 (19.7%) | 40 (17%) |
| Complete | 9 (3.8%) | 11 (4.7%) |
| Partial | 38 (15.9%) | 29 (12.3%) |
| Platinum-Refractory | | |
| n | 130 | 124 |
| Total | 16 (12.3%) | 8 (6.5%) |
| Complete | 1 (0.8%) | 1 (0.8%) |
| Partial | 15 (11.5%) | 7 (5.6%) |
| Platinum-Sensitive | | |
| n | 109 | 111 |
| Total | 31 (28.4%) | 32 (28.8%) |
| Complete | 8 (7.3%) | 10 (9.0%) |
| Partial | 23 (21.1%) | 22 (19.8%) |

Figure #4: Kaplan-Meier Curve of Progression-free Survival (Intent-to-treat Ovarian Cancer Population)



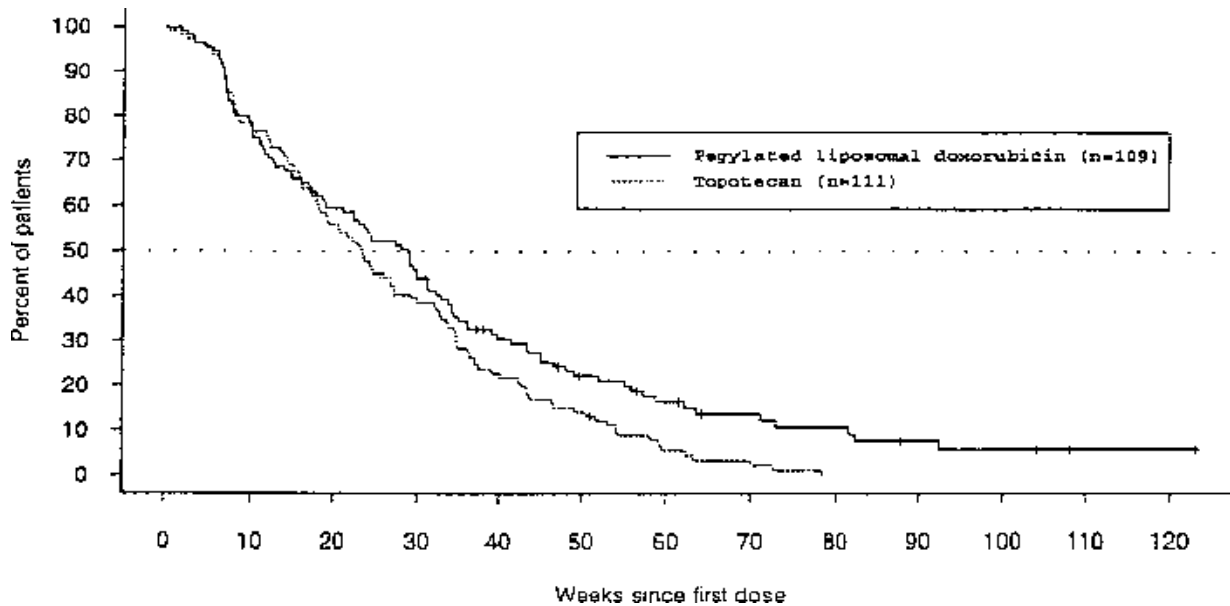
For the entire ITT population, overall survival for CAELYX was at least equivalent totopotecan with ratio of 1.121 (90% CI 0.920-1.367, $P=0.34$) in favor of CAELYX.

In the protocol-defined ITT population platinum-sensitive subgroup (patients who responded to initial platinum-based therapy and had a progression-free interval of greater than 6 months off treatment), both time to progression and overall survival were significantly in favor of CAELYX (Table 19).

Table 19 - Pivotal Phase III Study Protocol 30-49 (Ovarian Cancer Patients)

| Time to Progression for Platinum-Sensitive Subgroup of ITT population | | | | |
|---|-----|---------------|-------------------|---------------|
| Treatment | n | Median (days) | Hazard Ratio (HR) | 90% CI for HR |
| CAELYX | 109 | 202 | 1.349 | 1.065 - 1.709 |
| Topotecan | 111 | 163 | | |
| Overall Survival for Platinum-Sensitive Subgroup of ITT population | | | | |
| CAELYX | 109 | 756 | 1.72 | 1.222 - 2.422 |
| Topotecan | 111 | 498 | | |

Figure #4: Kaplan-Meier Curve of Progression-free Survival (Intent-to-treat Population; Platinum-Sensitive Ovarian Cancer Patients).



A consistent trend favouring CAELYX was demonstrated across efficacy endpoints and prognostic subgroups.

Pivotal Phase III Study-Safety

Overall, treatment-related adverse events observed with CAELYX tended to be of mild or moderate severity.

The most common drug-related adverse events associated with CAELYX were PPE (Palmar-Plantar Erythrodysesthesia) and stomatitis and were severe in 23% and 8% of CAELYX-treated patients respectively. Both were easily managed with dose reduction or delays and were seldom treatment-limiting or life-threatening.

The most common drug-related adverse events associated with topotecan were hematologic toxicities (neutropenia, anemia, thrombocytopenia, leukopenia), nausea and alopecia.

Hematologic events, nausea, and alopecia were less frequent and less severe with CAELYX compared with topotecan. Hematologic toxicity with topotecan was frequently associated with clinical sequelae, such as infection, or the need for transfusions or hematopoietic growth factors.

Table 20 - Most Frequently Reported Treatment-Related Adverse Events for Each Ovarian Cancer Treatment Group - Phase III Study

| | CAELYX (n=239) | | Topotecan (n=235) | |
|------------------|----------------|-----------------------|-------------------|-----------------------|
| | All Severities | Grade III/IV Severity | All Severities | Grade III/IV Severity |
| Neutropenia | 84 (35%) | 29 (12%) | 191 (81%) | 178 (76%) |
| Anemia | 85 (36%) | 13 (5%) | 169 (72%) | 66 (28%) |
| Thrombocytopenia | 31 (13%) | 3 (1%) | 152 (65%) | 80 (34%) |
| Leukopenia | 87 (36%) | 24 (10%) | 149 (63%) | 117 (50%) |
| Alopecia | 38 (16%) | 3 (1%) | 115 (49%) | 14 (6%) |
| PPE* | 117 (49%) | 55 (23%) | 2 (1%) | 0 |
| Stomatitis | 95 (40%) | 20 (8%) | 35 (15%) | 1 (0.4%) |
| Nausea | 85 (36%) | 7 (3%) | 127 (54%) | 14 (6%) |

* PPE = Palmar-plantar erythrodysesthesia

There was no evidence of a relationship between cumulative CAELYX dose and change from baseline for LVEF (Left Ventricular Ejection Fraction).

When quality of life outcomes such as toxicity and progression are considered, CAELYX is always preferred over topotecan as demonstrated in the quality-adjusted survival analysis.

Although pain secondary to palmar-plantar erythrodysesthesia (PPE) is more common in CAELYX treated patients, this rarely resulted in study discontinuation.

AIDS-KS

Efficacy data on refractory patient population

CAELYX was studied in an open-label, single-arm, multicenter study utilizing CAELYX at 20 mg/m² by intravenous infusion every three weeks generally until progression or intolerance occurred. In an interim analysis, the treatment history of 383 patients was reviewed, and a cohort of 77 patients was retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least two of three treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy. Of the 77 patients selected, 66 had disease progression on conventional chemotherapy prior to entering the trial and 11 could not continue systemic chemotherapy because of intolerable toxicity. These 77 patients were predominantly white, homosexual males with a mean age of 38 years.

Two analyses of tumor response were used to evaluate the effectiveness of CAELYX:

- 1- Indicator Lesion Assessment: A retrospective analysis was conducted based on analysis of five indicator lesions. A partial response was defined as a decrease of $\geq 50\%$ in the total size of the indicator lesions compared to study entry, or a decrease of 50% in the number of raised lesions.
- 2- Investigator Assessment: Investigator assessment of response was based on ACTG criteria. Partial response was defined as no new lesions, sites of disease, or worsening edema. In addition, one of the following criteria had to be fulfilled: (1) a 50% or greater decrease in the number of all previously existing lesions; (2) a complete flattening of at least 50% of all previously raised lesions; (3) a 50% decrease in the sum of the products of the largest perpendicular diameters of the indicator lesions; or (4) the patient met the criteria for Clinical Complete Response except the patient had residual tumor-associated edema or effusion.

Analyses of efficacy were conducted using both conventional (“best”) and “conservative” response methodologies for the 77 refractory patients. According to the “conservative” response methodology (updated ACTG response criteria), patients had to meet the response criteria at a minimum of two consecutive clinical evaluations, separated by a minimum of 21 days, with no record of prior disease progression. The results obtained using both of these methodologies are summarized below:

Table 21 - Best Response in Refractory^a AIDS-KS

| | Indicator Lesion Assessment | Investigator Assessment |
|---------------------------------|------------------------------------|--------------------------------|
| Number of Patients | 77 | 77 |
| Best Response | | |
| Complete | 0 | 1 (1.3%) |
| Partial | 52 (67.5%) | 43 (55.8%) |
| Stable | 20 (26.0%) | 29 (37.7%) |
| Progression | 5 (6.5%) | 4 (5.2%) |
| Time to PR and/or CR (days) | | |
| Median | 69 | 94 |
| Range | 1-351 | 1-280 |
| Duration of PR and/or CR (days) | | |
| Median | 64 | 113 |
| Range | 1-211 | 15-368 |

^a Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

PR = Partial response; CR = Complete response

Table 22 - Best “Conservative” Response in Refractory^a AIDS-KS

| | Indicator Lesion Assessment | Investigator Assessment |
|---------------------------|------------------------------------|--------------------------------|
| Number of Patients | 77 | 77 |

| | | |
|---------------------------------|------------|------------|
| Best Response | | |
| Complete | 0 | 1 (1.3%) |
| Partial | 26 (33.8%) | 33 (42.9%) |
| Stable | 19 (24.7%) | 22 (28.6%) |
| Progression | 32 (41.6%) | 21 (27.3%) |
| Time to PR and/or CR (days) | | |
| Median | 92 | 99 |
| Range | 1-414 | 1-304 |
| Duration of PR and/or CR (days) | | |
| Median | 65 | 113 |
| Range | 22-211 | 21-368 |

^aPatients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

PR = Partial response; CR = Complete response

Controlled Trials

Two phase III, randomized, multicenter trials have been performed, comparing CAELYX at a dose of 20 mg/m² with a combination chemotherapy regimen of 20 mg/m² Adriamycin[®], 10 U/m² bleomycin and 1.0 mg vincristine (ABV) or 15 U/m² bleomycin and 1.4 mg/m² vincristine (BV) in the treatment of severe AIDS-KS. Patients received up to 6 cycles of either treatment regimen every 2 weeks (ABV-controlled) or 3 weeks (BV-controlled). Patients with extensive and progressive cutaneous KS lesions or mucocutaneous disease and/or documented visceral disease were enrolled in these studies. Most patients had between 10-50 lesions at baseline and CD4 counts of less than 50 cells per mm³. A total of 499 patients were treated in these two studies: 254 with CAELYX, 125 with ABV, and 120 with BV.

The primary efficacy parameter used in studies 30-10 and 30-11 was overall clinical assessment as determined by the investigator. Tumor response was to be classified as complete, clinically complete, partial, stable disease, or progressive disease, based on a refinement of the ACTG criteria published in 1989. In order to be classified as a “responder” (partial response (PR), clinical complete response (CCR), or complete response (CR)), the patient must have had at least two sequential investigator assessments, at least 28 days apart, that consistently confirmed the response. Partial response was defined as above (see efficacy data on refractory patient population; definition of investigator assessment). In conjunction with investigator assessment, additional assessments were also made, among which, assessment of indicator lesion characteristics and quality of life (QOL) questionnaires. Primary efficacy results are summarized below:

Table 23 - Controlled Trials - Response Summary

| | CAELYX | ABV | BV |
|-------------------------------|------------------|------------------|------------------|
| | (N = 254) | (N = 125) | (N = 120) |
| Complete/Partial Response | 132 (52.0%) | 31 (24.8 %) | 28 (23.3%) |
| Time to CR/PR - Median (Days) | 43 | 50 | 64 |

| | | | |
|--------------------------|-----|----|-----|
| Duration - Median (Days) | 119 | 92 | 123 |
|--------------------------|-----|----|-----|

CR = Complete response; PR = Partial response

As evaluated by investigator assessment, the overall (complete/partial) response rate for CAELYX was significantly ($P < 0.001$) superior to that of ABV and BV. In the CAELYX group, 8 patients (3.1%) achieved a clinical complete response and 124 patients (48.8%) achieved a partial response. In the ABV group, no patients achieved a clinical complete response and 31 (24.8%) achieved a partial response; in the BV group, 1 patient (0.8%) achieved a clinical complete response and 27 (22.5%) achieved a partial response.

Response in both the CAELYX patients and the control arms was associated with significant improvements in the characteristics of the KS lesions, including a reduction in lesion thickness and nodularity, improvement in lesion color, and resolution of lesion-associated edema.

CAELYX patients also showed a mean decrease of indicator lesion size by 26.0% by the end of treatment. ABV patients showed a mean decrease of 14.6%, whereas BV patients showed a slight increase (0.2%). Compared to ABV and BV treatment, the response rates achieved by CAELYX also translated into improved QOL for patients.

Cardiotoxicity

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses $>450 \text{ mg/m}^2$ body surface, or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on ten AIDS-KS patients receiving cumulative doses of CAELYX greater than 460 mg/m^2 body surface, indicate no evidence of anthracycline-induced cardiomyopathy in 5 patients, minimal myocardial cell damage ($<5\%$) in 4 patients and in 1 patient cell damage was $>6-15\%$. The recommended dose of CAELYX for AIDS-KS patients is 20 mg/m^2 body surface, every two-to-three week. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients ($>400 \text{ mg/m}^2$ body surface) would require more than 20 courses of CAELYX therapy over 40 to 60 weeks.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Therapeutic Efficacy of CAELYX

The efficacy of CAELYX, equivalent doses of conventionally formulated doxorubicin hydrochloride and doxorubicin hydrochloride encapsulated in conventional liposomes have been compared in a variety of murine tumor models including several human xenograft models. In every model examined, CAELYX was more effective than the same dose of doxorubicin hydrochloride in inhibiting or halting tumor growth, in effecting cures and/or in

prolonging the survival of tumor-bearing animals; and in no case was CAELYX less effective than doxorubicin hydrochloride. CAELYX was more active in both solid and dispersed tumors and was more effective than doxorubicin hydrochloride in preventing spontaneous metastases from intramammary implants of two different mammary tumors in mice. In two tumor models in which they were compared, CAELYX was also more effective than the same dose of doxorubicin hydrochloride encapsulated in non-pegylated liposomes, demonstrating the impact of the long-circulating liposome.

Pharmacokinetics

Single dose studies were performed in rats and dogs, and multiple dose pharmacokinetic studies were also conducted in rats, rabbits and dogs to characterize the plasma pharmacokinetics of CAELYX.

The plasma pharmacokinetics of CAELYX and doxorubicin were found to be significantly different in all species evaluated. The plasma concentration of doxorubicin was up to 2000-fold higher in CAELYX-treated animals after intravenous injection of equivalent doses of CAELYX and doxorubicin hydrochloride. Plasma concentration by time data were best fit with a bi-exponential curve, with a relatively short first phase (half-life = 1 to 3 hours), and a more prolonged second phase, which represented the majority of the AUC (area-under-the-curve), and a half-life ranging from 20 to 30 hours. The volume of distribution was smaller, and clearance was substantially decreased when compared to doxorubicin hydrochloride. Although plasma concentration and AUC were dose-dependent, CAELYX disposition kinetics were independent of dose. No evidence of drug accumulation was seen in dogs treated with up to 1.0 mg/kg of CAELYX every three weeks. The plasma pharmacokinetics of CAELYX in rats did not change with repeated dosing.

Despite the higher plasma concentration of doxorubicin after CAELYX treatment, the stability of the STEALTH[®] liposome and its low rate of doxorubicin release (leakage) in plasma results in very low levels of free (non-liposomal) doxorubicin hydrochloride in the bloodstream. Virtually the entire CAELYX dose administered to animals can be accounted for in the plasma in 2-5 minutes after treatment, suggesting that no sudden burst of drug release occurs after drug injection, as has been reported for conventional, non-STEALTH[®] liposomal formulations of doxorubicin hydrochloride. Direct measurements of the amount of liposomal drug in the plasma shows that more than 90% to 95% of the doxorubicin, remains encapsulated in liposomes.

Tissue levels of doxorubicin were determined in tumor-bearing mice and in non-tumor-bearing rats and dogs. In the tumor model studies, tumor AUC's in CAELYX-treated animals ranged from 7-fold higher in a murine C26 colon carcinoma model to 25-fold greater in the human prostatic xenograft than in mice treated with the same dose of doxorubicin hydrochloride.

Tumor and normal tissue levels of doxorubicin continued to rise for at least 24 hours in CAELYX-treated mice but peaked after 1-4 hours in animals that received doxorubicin hydrochloride, declining rapidly thereafter.

Doxorubicin concentrations persisted in the tissues in CAELYX-treated animals, owing to the slower clearance of liposome-associated drug, resulting in significantly higher tissue AUC's. It

is known that doxorubicin-associated toxicity, particularly cardiotoxicity, is associated with the high peak concentrations of doxorubicin, but not with AUC. Treatment regimens that minimize peak doxorubicin plasma concentrations, but maintain cumulative AUC, are associated with reduced risk of cardiomyopathy and do not compromise anti-tumor activity. The reduced cardiac tissue concentrations in CAELYX-treated animals correlate well with the observation that CAELYX is less cardiotoxic than doxorubicin hydrochloride in animals (see [16 NON CLINICAL TOXICOLOGY, Special Toxicology, Cardiotoxicity](#)).

The higher AUC's in the tissues also did not correlate with increased toxicity, with the exception of cutaneous lesions. Doxorubicin concentrations were higher at sites of cutaneous lesions than in normal skin, with levels falling rapidly after treatment stopped and nearing the concentrations found in normal skin by the end of the recovery period. It could not be determined if lesions formed because of increased doxorubicin concentrations, or whether doxorubicin concentration was secondarily increased as a result of extravasation of CAELYX at pre-existing sites of tissue damage. Studies in dogs have demonstrated that the incidence and severity of the cutaneous lesions is related to dose intensity, with lower dose levels associated with decreased lesion formation (see [16 NON CLINICAL TOXICOLOGY, Special Toxicology, Dermal Lesion Development](#)).

General Toxicology:

Acute Toxicity

In single dose studies, the acute toxicity of CAELYX was similar for mice, rats, and dogs. In the rat, the incidence and severity of clinical observations were dose-related and included tail and footpad lesions, swelling and inflammation of the penis and scrotum, rough haircoat, alopecia, hypoactivity, hunched posture, respiratory distress, and reduced body weight gain. Reversible myelotoxicity was noted based on decreased RBC, WBC, hemoglobin, and hematocrit. Increases occurred in BUN and cholesterol levels.

Dogs were the most sensitive species. Treatment-related toxicity included dermal toxicity, reversible myelotoxicity, hematologic changes, increased BUN, gastrointestinal toxicity, body weight loss, reversible cutaneous lesions, and alopecia. Myelotoxicity was less severe compared with the doxorubicin hydrochloride group.

In a single dose study, MPEG-DSPE micelles, a component of the CAELYX liposome formulation, had no acute toxic effects in mice when administered at a lipid dose approximately 30-fold that found in the dose of 20 mg/m² recommended for humans.

Long-term Toxicity

The toxicity of CAELYX following repeated administration was similar in rats and dogs and an extension of the findings in the acute studies. Treatment-related effects included dermatologic toxicity, body weight and food consumption changes, alopecia, myelotoxicity (bone marrow cellularity changes), and hematologic effects (leukopenia and lower erythron mass). Dogs also

showed gastrointestinal toxicity and no pathologic signs of toxicity. In the long-term studies, CAELYX was compared with non-liposomal doxorubicin hydrochloride:

Table 24 - Comparative Long-term Toxicity Studies

| Species | No./ Sex | No. of Doses | Dose (mg/kg) | CONCLUSIONS |
|---------|--------------------------------------|----------------|---|--|
| Rat | Groups of 30 15 Female 15 Male | 13 dose q3d | <u>CAELYX</u> 0.25, 1.0, 1.5 <u>Dox-</u> <u>hydrochloride</u> 1 | <ul style="list-style-type: none"> • Dosing halted in 1.5 mg/kg CAELYX group due to effect of dermal lesions on general health. Death of 1/10 males related to this toxicity. • CAELYX induced dermal lesions at ≥ 1 mg/kg; readily reversible upon cessation of treatment. • CAELYX less cardiotoxic, hemotoxic and nephrotoxic than equivalent dose of doxorubicin hydrochloride. • Other adverse effects similar in nature, incidence and severity in CAELYX and doxorubicin hydrochloride groups. • No effect of placebo liposomes. |
| Dog | Groups of 6 Male | 4 dose q7d | <u>CAELYX</u> 1 <u>Dox-</u> <u>hydrochloride</u> 1 | <ul style="list-style-type: none"> • 1 CAELYX and 1 Dox-hydrochloride animal died during treatment. • Myelotoxicity milder in CAELYX groups, with later onset, less severe changes and quicker recovery. • CAELYX induced adverse inflammatory lesions of feet and legs; readily reversed upon cessation of treatment. • Other adverse effects comparable in CAELYX and Dox-hydrochloride treatment. • Dogs given placebo liposomes exhibited transient hypoactivity, flushing, emesis, prostration during 2nd dose. Reduced in incidence and severity at 3rd and 4th doses. |

| | | | | |
|-----|---------------------------------|-----------------|--|--|
| Dog | Groups of 6 Female 6 Male | 10 dose q21d | <u>CAELYX</u> 0.25, 0.75, 1.0 <u>Dox-</u> <u>hydrochloride</u> 1.0 | <ul style="list-style-type: none"> • Mild to moderate cardiomyopathy in all dogs treated with non-liposomal doxorubicin hydrochloride that worsened during the recovery period. • No evidence of cardiotoxicity in any CAELYX-treated dog at interim or final necropsy. • Bone marrow hypocellularity in ribs and femur of doxorubicin hydrochloride-treated animals, with mild decreases in WBC count. Both resolved in 4-week recovery period. WBC depression only in CAELYX groups, also resolved in recovery period • Alopecia and mild dermal ulcers seen in 0.75 and 1.0 mg/kg CAELYX groups. Ulcers healed, but alopecia only partially resolved during recovery. • Placebo liposome effect (hypoactivity, emesis, etc.) could be controlled by reducing dose rate from 2.0 to 0.5 mL/min. |
|-----|---------------------------------|-----------------|--|--|

Carcinogenicity:

Doxorubicin, the active component of CAELYX, is both mutagenic and carcinogenic so conducting carcinogenicity and mutagenicity studies was not deemed necessary. Four studies were carried out with STEALTH® placebo liposome to confirm their lack of mutagenicity and genotoxicity.

Negative results were obtained in the Ames, the L5178Y mouse lymphoma, and chromosomal aberration assays *in vitro*, and the mouse bone marrow micronucleus assay *in vivo*.

Nephrotoxicity

Cynomolgus monkeys (3/sex) were administered a single intravenous dose of CAELYX (Doxil® formulation) of 10 mg/kg (120 mg/m²; approximately two times the clinical dose) and followed for 28 days as a comparator arm in an acute toxicity study with an investigational doxorubicin formulation. Three male and 1 female monkey were sacrificed on Day 11 or 15 in poor condition attributable to renal toxicity. Renal toxicity reflected in increased serum creatinine and blood urea nitrogen levels included tubular and/or glomerular changes and presented as renal hemorrhage and/or edema (cortex, pelvis or papilla), distal tubular dilatation, tubular protein casts, hypertrophy of the Bowman’s capsular epithelial cells, interstitial neutrophil infiltration, and/or necrosis of renal adipose tissue. Renal toxicity has been observed with even lower single doses of doxorubicin hydrochloride in rats and rabbits. However, since an evaluation of the post-marketing safety database for CAELYX in patients has not suggested a significant nephrotoxicity liability of CAELYX, these findings in monkeys may not have relevance to patient risk assessment.

Reproductive and Developmental Toxicology:

The potential developmental toxicity of CAELYX was evaluated in rats and rabbits. In the first study, intravenous bolus injections of CAELYX 0.1, 0.5, or 1.0 mg/kg was administered on gestation days 6, 9, 12, and 15; or STEALTH[®] placebo liposomes or saline on the same treatment schedule. An additional group received doxorubicin 0.2 or 0.4 mg/kg daily between gestation days 6 and 15. Equivalent maternal toxicity occurred in the CAELYX 0.5 and 1.0 mg/kg groups and in the doxorubicin groups. CAELYX 1.0 mg/kg induced decreased fetal weights, increases in fetal resorptions, and retarded ossification of caudal vertebrae and xiphoid centers in the fetuses. No adverse effects were seen in dams or fetuses in the placebo liposome or CAELYX 0.1 mg/kg groups.

The embryotoxicity of CAELYX was confirmed in the study in pregnant New Zealand White rabbits administered intravenous injections of CAELYX 0.5, 1.5, or 2.5 mg/kg on gestation days 6, 9, 12, 15, and 18. All doses were maternally toxic. Four females that died (3 and 1 in the high- and mid-dose groups, respectively), surviving females in the mid- and high-dose groups (4 and 2, respectively), and 4 females (low-dose group) who aborted prior to the end of the study all had 100% resorbed conceptuses. The uterine of another female (low-dose group) who aborted prior to the end of the study consisted of 3 normal conceptuses, 4 late resorptions, and 5 early resorptions. CAELYX is both embryotoxic and an abortifacient in rabbits.

Special Toxicology:

Local Tolerance

Two single dose studies were conducted to examine the potential of CAELYX to cause injury if accidentally extravasated. Rabbits received single intravenous or subcutaneous injections of 0.1 or 1.0 mL of undiluted CAELYX 2.0 mg/mL, doxorubicin hydrochloride 2.0 mg/mL, or STEALTH[®] placebo liposomes. Histopathological evaluation of the intravenous injection sites revealed that CAELYX, doxorubicin hydrochloride, and placebo liposomes were well tolerated with no gross or microscopic evidence of irritation.

Hemolytic Potential

The hemolytic potential of CAELYX and STEALTH[®] placebo liposomes in human blood was assessed *in vitro*, as well as their compatibility with human serum and plasma. Neither CAELYX 1.0 mg/mL nor empty STEALTH[®] liposomes induced hemolysis of human erythrocytes, nor did either cause coagulation or precipitation of human serum or plasma.

Lysophosphatidylcholine (LPC) is a degradation product of the phosphatidylcholine component of the liposomes. An additional hemolytic potential study using CAELYX formulations prepared with 0 mg/mL, 0.5 mg/mL, or 0.88 mg/mL LPC caused no hemolysis of rat blood cells.

Dermal Lesion Development

The effect of peak dosage and dose frequency on dermal lesion development and myelosuppression was studied in dogs. CAELYX 0.5, 1.0, 1.5 mg/kg was administered q7d,

q14d, or q28d by intravenous (cephalic) catheter for 6-12 weeks. The higher dose intensities with lower dose frequency (1.0 mg/kg q14d and 1.5 mg/kg q28d) produced minimal evidence of cyclic depression of hemoglobin and hematocrit. In both groups, the hemoglobin and hematocrit values recovered to prestudy values at the end of the study. The onset of lesions occurred within 1 to 2 weeks after initiation of treatment and began to heal at rates that varied depending on lesion severity and dose frequency.

Myelosuppression was mild with all treatment regimens and no evidence of treatment-related leukopenia was observed. Dosages of 0.5 mg/kg given every 2 or 4 weeks were tolerated much better than the weekly doses at 0.5 mg/kg. Comparison of groups that received 0.5 mg/kg/treatment showed clear dose frequency-related effects on lesion development, lesion severity, and general toxicity. Integration of current results with previous studies showed a similar frequency-dependent effect with 1.0 mg/kg; weekly and every 2-week regimens produced severe toxicity while a 3-week dose cycle was better tolerated.

Cardiotoxicity

Cardiotoxicity is frequently observed in animals and man administered non-liposomal doxorubicin. However, in studies with CAELYX in rats and dogs it was observed that cardiotoxicity was either absent or present at a substantially decreased incidence and severity. A multiple-dose study was carried out to evaluate the relative cardiotoxicity of CAELYX and doxorubicin hydrochloride administered to male rabbits by intravenous injection q5d for targeted cumulative dosages of 14 or 21 mg/kg. Treatment was interrupted twice for 26 days to allow recovery from short-term toxicities unrelated to cardiotoxicity. Necropsies were conducted 1, 5, and 13 weeks after the 14th dose and 13 weeks after the 21st dose; hearts were examined for histopathological changes at each point. Lesion severity and incidence at five sites within the heart were also utilized to calculate a cardiotoxicity score for each animal.

Nine early deaths occurred in the CAELYX group, 3 due to cardiotoxicity and 5 due to generalized stress secondary to dermal lesions; 5 early deaths occurred in the doxorubicin hydrochloride group, all with evidence of cardiotoxicity. Cardiac lesions were more severe and frequent in the doxorubicin hydrochloride group: overall, 4/25 (16%) CAELYX-treated animals with cardiotoxicity compared to 10/15 (67%) doxorubicin hydrochloride-treated animals. The decreased cardiotoxicity was not due to increased latency of the lesion; there was no significant increase in lesion incidence or severity with time post-treatment. Cardiomyopathy increased in evidence and severity with time after treatment in the doxorubicin hydrochloride treatment group. Up to 50% more CAELYX (21 mg/kg cumulative dose) could be given without incurring increased cardiotoxicity compared to doxorubicin hydrochloride (14 mg/kg cumulative dose).

STEALTH® Liposome Placebo

In addition to the mutagenicity and developmental studies, and the acute and long-term studies in which placebo liposomes were used as controls, STEALTH® Liposome Placebo was evaluated for its potential to induce cardiovascular changes in dogs and neurobehavioral changes in rats. In the cardiovascular study, dogs showed a significant decrease in blood pressure (19-70%) immediately after the start of dosing followed by a rapid partial recovery

after the end of dosing, and a return to normal values within 4-6 hours post-dose. Compensating acceleration in heart rate was not seen. The dose rate did not affect the extent of hypotension, but inversely affected the duration. In the rat study, placebo liposomes did not induce any adverse neurobehavioral effects or evidence of neurotoxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCAELYX®

Pegylated Liposomal Doxorubicin Hydrochloride for Injection

Read this carefully before you start taking CAELYX. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about CAELYX.

Serious Warnings and Precautions

- CAELYX should be prescribed and administered by a healthcare professional specialized in the use of cancer drugs.
- Possible serious side effects with the use of CAELYX include:
 - Heart damage, including congestive heart failure and weakening of heart muscle;
 - Sudden reactions to the administration of the drug. These can be allergic-like reactions and can be serious or life threatening;
 - Decrease of blood cell production (myelosuppression);
 - Developing secondary oral cancer. This is a form of cancer that spread from the original cancer and developed in another part of the body. Secondary oral cancer can be fatal.

What is CAELYX used for?

CAELYX is used in adults to treat:

- Metastatic breast cancer, a form of cancer that has spread to other parts of the body. CAELYX is used when the patient is at risk of developing heart problems if treated with doxorubicin;
- Advanced ovarian cancer. CAELYX is used when standard first-line chemotherapy treatment does not work.
- AIDS-related Kaposi's sarcoma. CAELYX is used in patients who have a low number of a specific type of white blood cell (CD4 lymphocytes) and:
 - have large areas of the skin and mucous membrane impacted, or ;
 - have internal organ disease which has worsen even with therapy, or;
 - who are not able to tolerate previous combination chemotherapy that targets the entire body.

How does CAELYX work?

CAELYX contains an ingredient which is able to interact with your body in such a way as to selectively kill cancer cells. Doxorubicin hydrochloride, the medicinal ingredient in CAELYX, is surrounded in tiny spheres called pegylated liposomes. Pegylated liposomes help deliver the medicinal ingredient from the blood stream to the cancerous tissue in your body.

What are the ingredients in CAELYX?

Medicinal ingredients: Doxorubicin hydrochloride

Non-medicinal ingredients: ammonium sulfate, cholesterol, histidine, hydrochloric acid, hydrogenated soy phosphatidylcholine (HSPC), N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), sodium hydroxide, sucrose and water for injection

CAELYX comes in the following dosage forms:

suspension: 2 mg/mL

Do not use CAELYX if:

- you are allergic to doxorubicin hydrochloride, any of the other ingredients in CAELYX or components of the container.
- you are breast-feeding.
- you think you are pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CAELYX. Talk about any health conditions or problems you may have, including if you:

- have had previous treatment with anthracyclines, a class of drug used in cancer chemotherapy (e.g. doxorubicin, epirubicin, etc.)
- are undergoing chest radiation
- have heart and blood vessel problems
- have liver problems or disease
- are diabetic. CAELYX contains sugar which may require an adjustment to the treatment of your diabetes
- have a history of myelosuppression;

Other warnings you should know about:

Monitoring and tests: Your healthcare professional will:

- complete blood tests to monitor your blood cell count during your treatment.
- monitor your heart function during your treatment
- monitor your liver function before administering CAELYX
- examine your mouth for cancer during your treatment. You may develop oral cancer that can be fatal.

Hand-Foot Syndrome: Treatment with CAELYX can increase your risk of developing Hand-Foot Syndrome. To prevent and treat this condition, considering the following:

- Soak hands and/or feet in basins of cold water when possible (e.g., while watching television, reading, or listening to the radio);
- Keep hands and feet uncovered (no gloves, socks, etc.);
- Stay in cool places (under tree shade, by a swimming area with shade etc.);
- Take cool baths or stay in the water during the summer;
- Avoid vigorous exercise that might cause trauma to the feet (e.g. jogging);
- Avoid exposure of skin to very hot water (e.g., jacuzzis, saunas);
- Avoid tight-fitting footwear or high-heeled shoes

Lung Problems: You may develop Interstitial Lung Disease (ILD) while taking CAELYX. ILD is a lung disease that inflame or scar lung tissue. ILD can be fatal and your healthcare professional may end your treatment if you develop this condition.

Driving and using machines: Do not drive or operate any tools or machines if you feel tired or sleepy from treatment with CAELYX.

Female Patients:

- If you are pregnant, or able to get pregnant there are specific risks you must discuss with your healthcare professional
- Do not take CAELYX while pregnant as it may harm your unborn child. Use effective contraception while taking CAELYX and for up to eight months after your last dose of CAELYX.
- CAELYX may pass into breast-milk. Do not breastfeed while you are taking CAELYX.

Male Patients:

Use effective contraception while taking CAELYX and for six months after your last dose of CAELYX.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CAELYX:

- other cancer treatments
- Drugs known to interact with the conventional formulation of doxorubicin hydrochloride.

How to take CAELYX:

- CAELYX will be given to you by your healthcare professional in a drip (infusion) into a vein. This may take from 30 minutes to more than one hour (i.e., 90 minutes)

Usual dose:

The usual dose of CAELYX is different for everyone. Your healthcare professional will calculate how much CAELYX to give you. Your dose will depend on the condition you are being treated for, your height and weight.

Overdose:

Overdosing worsens side effects like sores in the mouth.

If you think you, or a person you are caring for, have taken too much CAELYX, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

What are possible side effects from using CAELYX?

These are not all the possible side effects you may have when taking CAELYX. If you experience any side effects not listed here, tell your healthcare professional.

- Constipation
- Diarrhea
- Discomfort
- Loss of appetite
- Stomach pains/sickness (nausea or vomiting)
- Weight loss

CAELYX can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

| Serious side effects and what to do about them | | | |
|--|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| COMMON | | | |
| Allergic reactions: Flushing of the face, shortness of breath, headache, chills, chest pain, back pain, fever, sweating, tightness in the chest and/or throat, low or high blood pressure, dizziness and puffing of the face, stinging or swelling of the skin at the site of injection, tongue inflammation, general swelling, inflammation or eruption of skin. | | √ | |
| Fungal Infections: Oral thrush (creamy white, sore patches in your mouth or on your tongue); aching muscles with high temperature, sore throat, and swollen glands. | | √ | |
| Injection site reactions: rash, the drip stings or hurts while you are receiving a dose of CAELYX, uncontrolled shaking . | | √ | |
| Hand-foot syndrome: swelling, reddening painful skin and sores on the palms of your hands and feet. | | √ | |
| Heart problems: Irregular heartbeat, weakening of the heart muscle and/or swelling of feet or hands. | | √ | |
| Lung problems: Coughing, shortness of breath or difficulty in breathing which may be linked to infections you have caught as a result of your disease. | | √ | |
| Blood cancers: Fever (increased temperature) or any other sign of an infection, bruising more easily than normal, signs of anemia (reduction in red blood cells) such as tiredness, being short of breath, | | √ | |

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| and looking pale; decrease in the number of white blood cells, which can increase the chances of infections. | | | |
| Stomatitis (sore or inflammation inside of the mouth): Mouth sores/cold sores, pain in mouth. | | √ | |
| Eye and Nose problems: Blurred vision, tearing of the eye, sores in nose, bleeding from your nose. | | √ | |
| General feeling of tiredness, weakness, bone pain, breast pain, muscle pain, leg cramps or swelling. | √ | | |
| Skin reactions: Hair loss, inflammation of hair follicles, scaly skin, abnormal skin pigmentation, nail problems, pain, redness and dryness of skin . | √ | | |
| Nervous system problems: Feeling of pins and needles or pain in hands and feet; sleepiness, confusion. | | √ | |
| UNCOMMON | | | |
| Cellulitis (bacterial skin infection): Swelling, warmth, or tenderness in the soft tissues of your leg, sometimes with pain which gets worse when you stand or walk. | | √ | |
| RARE | | | |
| Leukemia (Cancer of the blood): Fatigue, breathlessness, infections, and bruising or bleeding more easily. | | √ | |
| Myelodysplastic Syndrome (Bone marrow disease affecting blood cells): Light-headedness, easy bruising or bleeding, fever, frequent infections and bone pain. | | √ | |

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| UNKNOWN | | | |
| Oral cancer: Mouth lining discolouration. | | √ | |
| Interstitial lung disease: Coughing and shortness of breath, possibly accompanied by fever, that is not brought on by physical activity. | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep CAELYX out of reach and sight of children.

Do not use if CAELYX dispersion is discolored or shows evidence of precipitation or particles.

CAELYX should be stored in the refrigerator (2 °C to 8 °C). Do not freeze. Discard partially used vials.

Diluted CAELYX should be refrigerated and used within 24 hours,

If you want more information about CAELYX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes

this Patient Medication Information by visiting the Health Canada website:
(<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <https://www.baxter.ca>,
or by calling 1-800-387-8399.

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