EU RISK MANAGEMENT PLAN

For Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion (pegylated liposomal doxorubicin hydrochloride)

Version 6.3

Issued 20 NOV 2023

Details of current RMP submission

RMP version to be assessed as part of this application	6.3
Data lock point for this RMP	12 SEP 2023
Date of final sign-off	20 NOV 2023
Rationale for submitting updated RMP	The RMP is being updated due to an authority request (procedure EMEA/H/C/PSUSA/00001172/202111) to update the safety concern profile to align to European Medicines Agency (EMA), Good Pharmacovigilance Practices (GVP) Module V Revision 2 requirements.

Other RMP versions under evaluation

Not applicable; there are currently no other Risk Management Plan (RMP) versions for Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion (hereafter Caelyx pegylated liposomal) under evaluation in the European Union (EU).

Details of the currently approved RMP

RMP version number	5.0[a]
Approval procedure number	EMEA/H/C/000089/II/0066
Date of approval (opinion date)	11 SEP 2014

[a] The EU RMP version 5.0 was developed by Janssen-Cilag International NV as the Marketing Authorization Holder (MAH) at the time. On 19 AUG 2019 Janssen notified the United States (US) Food and Drug Administration of the transfer of the US ownership and rights to Baxter Healthcare Corporation for Doxil (US tradename). On 23 DEC 2020 Baxter Healthcare Corporation entered into an agreement with Cilag GmbH International to acquire the global Marketing Authorization (MA) rights for Caelyx pegylated liposomal; MA transfer to Baxter Holding B.V. in the European Economic Area (EEA) was approved on 20 AUG 2021.

EU QPPV oversight

EU Qualified person responsible for pharmacovigilance (QPPV)/ QPPV Deputy name	Örjan Mortimer, MD/ Iva Slavcevova, MD
EU QPPV/ QPPV Deputy oversight declaration	The content of this RMP has been reviewed and approved by Baxter's QPPV or QPPV Deputy (by delegation). The electronic signature is available on file.

Summary of changes since last RMP approval

Part	Module/Annex	Version number of RMP when module/annex last approved	Sign-off date of last version approved	Summary of significant changes since last approval, if applicable
Part I	**Product(s) overview**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content aligned with the current Summary of Product Characteristics (SmPC).
Part II **Safety specification**	**SI:** **Epidemiology of the indication(s) and target population(s)**	4.0	21 JUN2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect updated epidemiology data and references.
	SII: **Non-clinical part of the safety specification**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
	SIII: **Clinical trial exposure**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
	SIV: **Populations not studied in clinical trials**	5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
	SV: **Post-authorization experience**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect updated post-marketing exposure data.
	SVI: **Additional EU requirements for the safety specification**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.

Part	Module/Annex	Version number of RMP when module/annex last approved	Sign-off date of last version approved	Summary of significant changes since last approval, if applicable
	SVII: **Identified and potential risks**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect removal of safety concerns.
	SVIII: **Summary of the safety concerns**	5.0	16 SEP 2013	Content revised to reflect removal of safety concerns.
Part III **Pharmacovigilance Plan (including post-authorization studies)**		5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect removal of safety concerns.
Part IV **Plans for post-authorization efficacy studies**		4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
Part V **Risk minimization measures**		5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect removal of safety concerns.
Part VI **Summary of the Risk Management Plan**		5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements. Content revised to reflect updated RMP.
Part VII **Annexes**	**Annex 1:** **EudraVigilance Interface**	4.0	21 JUN 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.

Part	Module/Annex	Version number of RMP when module/annex last approved	Sign-off date of last version approved	Summary of significant changes since last approval, if applicable
	Annex 2: **Tabulated summary of planned, ongoing, and completed pharmacovigilance study program**	5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
	Annex 3: **Protocols for proposed, ongoing, and completed studies in the Pharmacovigilance Plan**	5.0	16 SEP 2013	Edited to align format/content to EMA GVP Module V Revision 2 requirements.
	Annex 4: **Specific adverse drug reaction follow-up forms**	Not applicable	Not applicable	Not applicable
	Annex 5: **Protocols for proposed and ongoing studies in RMP Part IV**	Not applicable	Not applicable	Not applicable
	Annex 6: **Details of proposed additional risk minimization measures**	Not applicable	Not applicable	Not applicable
	Annex 7: **Other supporting data (including referenced material)**	4.0	21 JUN 2013	Content revised to reflect updated literature references.

Part	Module/Annex	Version number of RMP when module/annex last approved	Sign-off date of last version approved	Summary of significant changes since last approval, if applicable
	Annex 8: **Summary of changes to the Risk Management Plan over time**	5.0	16 SEP 2013	Content revised to reflect changes to the RMP.

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ABBREVIATIONS

Abbreviation	Definition
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ASR	Age-standardized rate
CD	Conventional doxorubicin
CD4	Cluster of Differentiation 4
CSR	Clinical study report
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
HCl	Hydrochloride
HIV	Human immunodeficiency virus
IV	Intravenous(ly)
kg	Kilogram(s)
KS	Kaposi's sarcoma
MA	Marketing Authorization
MAH	Marketing Authorization Holder
m^2	Square meter(s)
mm^3	Cubic millimeter(s)
mg	Milligram(s)
mL	Milliliter(s)
MPEG	Methoxypolyethylene glycol
MPS	Mononuclear phagocyte system
PARP	Poly ADP ribose polymerase
PL	Package Leaflet
QPPV	Qualified person responsible for pharmacovigilance
RMP	Risk Management Plan
RNA	Ribonucleic acid
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Doxorubicin hydrochloride in a pegylated liposomal formulation
Pharmacotherapeutic group(s) (ATC Code)	Cytotoxic agents (anthracyclines and related substances) (L01DB01)
Marketing Authorization Holder (MAH)	Baxter Holding B.V.
Number of medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** The active ingredient of Caelyx pegylated liposomal is doxorubicin hydrochloride (HCl), a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*.
	Summary of mode of action: The exact mechanism of the anti-tumor activity of doxorubicin is not known. It is generally believed that inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.
	Important information about its composition: Caelyx pegylated liposomal is doxorubicin HCl encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time. Excipients with known effect include fully hydrogenated soy phosphatidylcholine (from soyabean); use of Caelyx pegylated liposomal is contraindicated in patients with a known hypersensitivity.
Hyperlink to the product information	Approved SmPC: Caelyx pegylated liposomal Approved Package Leaflet (PL): Caelyx pegylated liposomal
Indication(s) in the EEA	**Current:** Caelyx pegylated liposomal is indicated: • As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk, • For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen,

	• In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant, • For treatment of acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) in patients with low Cluster of Differentiation 4 (CD4) counts (< 200 CD4 lymphocytes/cubic millimeter (mm^3)) and extensive mucocutaneous or visceral disease. Caelyx pegylated liposomal may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).
	Proposed: Not applicable; there are no proposed changes to the currently approved indications.
Dosage(s) in the EEA	**Current:** *Breast cancer/Ovarian cancer* Caelyx pegylated liposomal is administered intravenously (IV) at a dose of 50 milligrams (mg)/square meter (m^2) once every four weeks for as long as the disease does not progress and the patient continues to tolerate treatment. *Multiple myeloma* Caelyx pegylated liposomal is administered at 30 mg/m² on day 4 of a bortezomib 3-week regimen as a one-hour infusion administered immediately after the bortezomib infusion. The bortezomib regimen consists of 1.3 mg/m² on days 1, 4, 8, and 11 every three weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. *AIDS-related KS* Caelyx pegylated liposomal is administered IV at 20 mg/m^2 every 2-3 weeks. Avoid intervals shorter than 10 days as medicinal product accumulation and increased toxicity cannot be ruled out. Treatment of patients for 2-3 months is recommended to achieve a therapeutic response. Continue treatment as needed to maintain a therapeutic response. For additional posology details, including guidelines for Caelyx pegylated liposomal dose modifications to manage adverse events and use in special patient populations, refer to the SmPC.
	Proposed: Not applicable; there are no proposed changes to the currently approved dosages.
	Current:

Pharmaceutical form(s) and strength(s)	Pharmaceutical form: concentrate for solution for infusion Strength: 2 mg/milliliter (mL)
	Proposed: Not applicable, there are no proposed changes to the currently approved pharmaceutical form and strength.
Is/will the product be subject to additional monitoring in the EU	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication

Caelyx pegylated liposomal is indicated:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk,
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen,
- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant,
- For treatment of AIDS-related KS in patients with low CD4 counts (< 200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.

Caelyx pegylated liposomal may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

Incidence

Breast cancer

According to the European Cancer Information System, breast cancer continues to be the most common female cancer, with the incidence in the EU accounting for 29.2% of all cancers in women (Dafni 2019). In the EU, a total of 404,920 new female breast cancer cases were estimated to occur in 2018, corresponding to an age-adjusted standardized rate (ASR) of 144.9/100,000. The incidence is highest in the high economic European countries, which include most of Northern and Western Europe, along with Italy and Malta from Southern Europe (Dafni 2019). Incidence trends in the EU are mainly increasing. Breast cancer in males is more rare, however, similar to female breast cancer, the incidence rate continues to rise. The age-adjusted incidence rate has increased to 1.32 per 100,000 men in 2017, from 0.90 per 100,000 in 1980 as outlined by the Surveillance, Epidemiology, and End Results (SEER) (Howlader 2017). Multiple factors explain these

changes, including reproductive factors, increasing obesity and physical inactivity as well as increased screening intensity (European Commission 2020).

Ovarian cancer

Ovarian cancer is the seventh most common malignancy worldwide and the most lethal gynecological malignancy. The ASR of ovarian cancer incidence ranged from 3.0 to 11.4/100,000 women worldwide in 2012. The highest ASR was observed in Central and Eastern Europe, with 11.4/100,000 women in 2012 (Zhang 2019, ESGO 2018). A more recent study has found the highest incidence still found in Central and Eastern Europe (ASR = 10.7/100,000), followed by Northern Europe (ASR = 8.8/100,000), Polynesia (ASR = 8.8/100,000), North America (ASR = 8.1/100,000), and South East Asia (ASR = 8.1/100,000). The lowest incidence was observed in Central Africa (ASR = 4.4/100,000), the Caribbean (ASR = 4.6/100,000), and Southern Africa (ASR = 4.9/100,000) (Huang 2022).

Multiple myeloma

The global ASR for multiple myeloma varies between 0.54 and 5.3/100,000 population (Ludwig 2020). In the Western world (including Europe), the ASR has been reported to be approximately 5/100,000 (Kazandijan 2016). The lowest incidence rates were noted in Asia (0.54-1/100,000), and highest in New Zealand (5.3/100,000), followed by Australia (5.0/100,000), the United Kingdom (4.3/100,000), Israel, and Norway (both 4.2/100,000) (Ludwig 2020).

AIDS-related KS

A meta-analysis of publications found the crude overall KS incidence for Europe to be 589.84/100,000 person-years. When the study start time and participants were confined to post-1996 and adults, the KS incidence in Europe and North America decreased to 241.13 and 171.86/100,000, respectively (Liu 2018). A 2017 study based on over 200,000 patients reported raw KS incidence per 100,000 person-years in 42 cohorts from 57 countries, including North America (237/100,000), Latin America (244/100,000 person-years), Europe (180 per 100,000 person-years), Asia-Pacific (52 per 100,000 person-years) and South Africa (280 per 100,000 person-years) (The AIDS-defining Cancer Project Working Group 2017).

Prevalence

Breast cancer

Globally, as of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. Breast cancer in males is more rare in that makes up only approximately 1% of all breast cancers in the United States and worldwide (Zheng 2022). It is estimated that breast cancer accounts for 13.3% of all new cancer cases diagnosed in the EU in 2020 (WHO 2021).

Ovarian cancer

In 2020, a total of 313,959 new cases of ovarian cancer were recorded globally, and there were more than three quarters of a million women living within five years of their diagnosis (Reid 2023). Although ovarian cancer has a lower prevalence in comparison with breast cancer, it is more lethal due to asymptomatic and secret growth of the tumor, delayed onset of symptoms, and lack of proper screening that result in its diagnosis in the advanced stages (Bray 2018).

Multiple myeloma

Multiple myeloma accounts for 1% of all cancers and is the second most common hematologic malignancy after lymphoma (Palumbo 2011, Teras 2016, Siegal 2016). The estimated worldwide 5-year prevalence is approximately 230,000 patients (Kazandjian 2016). Its prevalence is expected to rise in Western countries in light of the aging population (Padala 2021).

AIDS-related KS

In the United States, KS was reported to be 20,000 times more frequent in patients with AIDS than in the general population and to be 300 times more frequent in patients with AIDS than in other immune-suppressed patient groups (Beral 1990). Similar patterns of KS risk were reported in Europe and Australia (Hermans 1996, Elford 1993). However, subsequent studies have shown that the rate of AIDS-related KS decreased significantly since the introduction of antiretroviral therapy (ART) in the 1990s (Cesarman 2019). Data from the EuroSIDA study, a prospective study of Human immunodeficiency virus (HIV)-1 infected patients that includes over 70 centers across Europe, was used to estimate the incidence of KS over time among HIV/AIDS patients. The incidence of KS decreased an estimated 39% annually between 1994 and 2003 (Mocroft 2004). In the United States, at the end of 2015, 1,904 persons with HIV (0.20%) had been diagnosed with KS in the previous 5 years (Peprah 2021).

Demographics of the population in the authorized indications and risk factors for the diseases

Breast and ovarian cancer

Approximately half of breast cancers develop in women who have no identifiable breast cancer risk factor other than gender (female) and age (over 40 years). Other factors that increase the risk of breast cancer include obesity, harmful use of alcohol/tobacco, family history of breast cancer, history of radiation exposure, reproductive history (such as age that menstrual periods began and age at first pregnancy), and postmenopausal hormone therapy (WHO 2021).

Risk factors associated with ovarian cancer include age (post-menopausal), race and socioeconomic status (usually found to be higher in White, affluent, and better-educated societies), nulliparity, family history of ovarian cancer, history of endometrial or breast cancer, use of hormone replacement therapy, and genetics (patients with BRCA1 and BRCA2 gene mutations) (Komodiki 2006).

Multiple myeloma

Risk factors for multiple myeloma include age, family history, sex and race. It is a neoplasm of older adults, and 1.5 times more common among men than women globally (Padala 2021). It is more than twice as common among African Americans with an incidence of 16.5/100,000 among African American men and 12.0/100,000 among African American women (compared to 8.2 and 5.0, respectively, for Caucasians) (Waxman 2010). Although the mutations that cause myeloma are acquired and not inherited, family history is a known risk factor for multiple myeloma. First-degree relatives of people with multiple myeloma have a 2 to 3 times higher risk of developing the disease (ASCO 2023).

AIDS-related KS

In patients with AIDS-related KS, the CD4 count appears to be an important factor associated with the development of the condition. For patients who presented with a new diagnosis of KS while on treatment with combined ART, the rate ratios for developing KS for patients with CD4 counts <200, 200 to 349, and 350 to 499 cells/mm^3 were 18.9, 3.6, and 4.1, compared with those with ≥500 cells/mm3 (Lodi 2010). Additional risk factors include sex (AIDS-related KS is predominantly a disease of males), concomitant infections (e.g., human herpesvirus-8 and other opportunistic infections) and concomitant

treatments (corticosteroid therapy has been associated with the induction of KS and the exacerbation of preexisting KS in persons living with HIV) (Groopman 2023a)

Main existing treatment options

Breast Cancer

The main treatment options for breast cancer include (National Cancer Institute 2023a)

- Hormone therapy - Depending on whether the patient is pre- or post-menopausal, treatment for women with metastatic breast cancer that is hormone receptor positive may include Tamoxifen therapy, aromatase inhibitor therapy, cyclin-dependent kinase inhibitor therapy, megestrol acetate, estrogen or androgen therapy, or anti-estrogen therapy such as fulvestrant.
- Targeted therapy - Treatment that uses drugs or other substances targeting specific proteins on cancer cells without harming normal cells, such as monoclonal antibody therapy, trastuzumab, pertuzumab, ado-trastuzumab, tyrosine kinase inhibitors, lapatinib, and poly ADP-ribose polymerase (PARP) inhibitors.
- Chemotherapy – Treatment can be administered orally, IV, intramuscularly, or placed directly into the cerebrospinal fluid, an organ or a body cavity; the administration method depends on the type and stage of the cancer. Chemotherapy may also be combined with immunotherapy.
- Surgery - Most patients with breast cancer have surgery to remove the cancer from the breast or other areas of the body where the cancer has spread. Treatment may be combined with chemotherapy, radiation therapy, and/or hormone therapy.
- Radiation therapy - External radiation and internal radiation may be used; the manner of administration depends on the type and stage of the cancer.

Ovarian cancer

Similar to treatment for breast cancer, treatment for ovarian cancer includes one or more of the following: surgery (e.g., hysterectomy, bilateral salpingo-oophorectomy, omentectomy), chemotherapy, hormone therapy, targeted therapy and/or radiation therapy. Choice of therapy depends largely on the stage of disease as well as general state of health, whether the patient plans to have children and other personal considerations (American Cancer Society 2018).

Multiple myeloma

Treatment for people with symptomatic myeloma includes both measures to control the disease as well as supportive care to improve quality of life, such as symptom relief and maintaining good nutrition. Standard treatments, which may be combined, include (ASCO 2023):

- Chemotherapy - Common drugs are melphalan, cyclophosphamide, doxorubicin, etoposide, cisplatin and bendamustine.
- Targeted therapy - Treatments include proteasome inhibitors (e.g., bortezomib), histone deacetylase inhibitors, monoclonal antibodies and nuclear export inhibitors.
- Immunomodulatory drugs - Thalidomide, lenalidomide (Revlimid), and pomalidomide (Pomalyst), which stimulate the immune system to keep new blood vessels from forming and feeding myeloma cells.
- Corticosteroids - Steroids, such as prednisone and dexamethasone, are very effective at reducing the burden of plasma cells, but this effect is only temporary.
- Immunotherapy - Cellular immunotherapies approved to treat multiple myeloma are idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti). These are chimeric antigen receptor T-cell therapies that target B-cell maturation antigens (a protein on the surface of myeloma cells).
- Stem cell transplant - The treatment involves using high-dose chemotherapy along with transfusion of previously collected immature blood cells (from patient or donor) to replace diseased or damaged marrow.
- Radiation therapy: This therapy may be used to quickly shrink myeloma cells in a specific area.

Thalidomide, lenalidomide, and bortezomib can also be effectively used as maintenance therapy to extend the disease's response to the initial therapy or after a bone marrow/stem cell transplant.

AIDS-related KS

KS patients are first treated with ART and then either a local and/or systemic therapy. The need for treatment beyond ART and the choice among the various options depend

upon the extent of disease, rapidity of tumor growth, HIV-1 viral load, CD4 cell count, and the patient's overall medical condition. Local therapies include radiation therapy, intralesional chemotherapy, cryotherapy, and topical retinoids. Systemic therapies include interferons and cytotoxic chemotherapy (single agent or combination regimens) (Groopman 2023b).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Breast cancer

Breast cancer was the leading cause of death from cancer in women (16.2% of cancer deaths) among 40 European countries in 2018 (Dafni 2019). Despite this statistic, studies have shown the mortality rate in the EU has declined from 15.0 in 2012 to 14.4 per 100,000 women in 2017 (-3.9%). Mortality rate predictions across Europe are expected to reach relatively uniform levels in 2025 (Wojtyla 2021).

Ovarian cancer

Ovarian cancer is more frequently diagnosed at an advanced stage, when its prognosis is poor, making this cancer the most lethal gynecological malignancy (Zhang 2019). There is wide variation in survival between histological groups, and stage at diagnosis remains an important factor in ovarian cancer survival. Survival from type I epithelial ovarian tumors for women diagnosed during 2005-2009 ranged from 40 to 70%, while survival from type II epithelial tumors was much lower (20-45%) (Matz 2017). Survival from germ cell tumors and sex-cord stromal tumors was higher than that of type II epithelial tumors. Survival from localized tumors was much higher than for advanced disease (80% vs. 30%) (Matz 2017). In Europe, ovarian cancer mortality declined over the past decade in all considered countries; reported rates were 4.3/100,000 (-13%) for all ages, 1.2/100,000 (-26%) at 20-49 years, 15.3/100,000 (-11%) at 50-69 years and 32.3/100,000 (-11%) at 70-79 years (Dalmartello 2022).

Multiple myeloma

In the past decade survival rates for multiple myeloma have improved significantly for the general population most likely due to the availability of effective therapy (Kristinsson 2007, Turesson 2010). It has been reported that median survival in patients with relapsed multiple myeloma prior to 2000 was 12 months compared to 24 months after 2000 (Kumar 2008). In another study, 5-year relative survival was found to increase from 34% in 1989-1992 to 56% in 2001-2005 periods of diagnosis (Schaapveld 2010). Siegal et al.

(2016) reported that 5-year relative survival rates in multiple myeloma improved to 49% for the 2005-2011 year period compared to 25% for 1975-1977 and 27% for 1987-1989.19 (Kazandjian 2016).

AIDS-related KS

The introduction of ART has led to a reduced incidence and improved survival of KS globally (Groopman 2023a, Groopman 2023b). The prognosis of patients with HIV or AIDS-related KS since the introduction of ART is illustrated by a consecutive series of 469 cases treated since 1998 at a single center (Bower 2014). Of these, 303 presented with T0 disease (65%) and 166 had T1 involvement (35%). Those with T0 disease generally were treated with ART alone, unless there was a need for symptomatic treatment of localized lesions, while those with T1 disease were managed with chemotherapy plus ART. For those with T0 disease, the overall five-year survival was 92% and for those with T1 disease the five-year survival was 83%.

Important co-morbidities

For the above indicated conditions, there are common comorbidities in the patient populations which may influence treatment, disease progression and prognosis. Common co-morbidities include:

- Breast and ovarian cancer - Cardiovascular conditions, diabetes, pain/inflammation, and renal disease (National Cancer Institute 2023b)
- Multiple myeloma - Cardiovascular conditions, renal disease, diabetes and hypertension (Sverrisdóttir 2021)
- AIDS-related KS – HIV/AIDS. As more people living with HIV and AIDS are accessing effective ART and living longer, as they age, they develop chronic age-related illnesses including cardiovascular conditions, diabetes and chronic kidney disease (Morales 2022).

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Caelyx pegylated liposomal (also marketed under Doxil trade name) was first approved in the United States on 17 NOV 1995. It differs from conventional doxorubicin (CD) due to the encapsulation of doxorubicin hydrochloride (the active pharmacological ingredient) in pegylated liposomes, which protects liposomes from detection by the MPS, consequently increasing its blood circulation time.

Non-clinical studies were conducted by previous MAHs; however, the safety pharmacology and toxicity profile of Caelyx pegylated liposomal is well-established as it has been marketed for over two decades. Historical data show the non-clinical safety profile of Caelyx pegylated liposomal has been characterized in single- and repeat-dose toxicity studies in rodents, dogs, and monkeys, as well as developmental toxicity and local tolerance studies. In most of these studies the effects of Caelyx pegylated liposomal were compared with those of CD.

On 23 DEC 2020 Baxter Healthcare Corporation entered into an agreement with Cilag GmbH International to acquire the global MA rights for Caelyx pegylated liposomal. The application for MA transfer to Baxter Holding B.V. in the EEA was approved by the EMA on 20 AUG 2021. As there have been no new non-clinical studies conducted by Baxter, the summary below presents historical non-clinical findings included in the previous RMP (version 5.0 issued 16 SEP 2013; prepared by Janssen-Cilag International NV), as well as relevant literature available in the public domain.

Key safety findings from non-clinical studies and relevance to human usage

Type of study		Key safety findings/Relevance to human usage
Toxicity	**Single-dose or acute toxicity**	Major findings in single-dose studies include myelotoxicity, gastrointestinal toxicity, and dermal toxicity. In a single-dose IV toxicity study conducted with Caelyx in rats, no mortality was observed at the dose of 8 mg/kg (EMA 2019).
	Repeat-dose toxicity	Major findings in repeat-dose toxicity studies were myelotoxicity, gastrointestinal toxicity, nephrotoxicity, dermal toxicity, and cardiotoxicity. These toxicities were less severe and at lower incidence compared with an equivalent dose of CD. In repeat-dose studies conducted in animals, the toxicity profile of Caelyx pegylated liposomal appears very similar to that reported in humans who receive long-term infusions of CD. However, the encapsulation of doxorubicin HCl in pegylated

Type of study		Key safety findings/Relevance to human usage
		liposomes results in the toxicity effects having differing strengths compared to CD.
	Reproductive/ Developmental toxicity	Caelyx pegylated liposomal resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kilogram (kg). Decreased testicular weights and hypospermia were present in rats after repeat doses of 0.25 mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day. Findings in repeat-dose toxicity studies indicate that Caelyx pegylated liposomal is likely to have a potential effect on human fertility. Caelyx pegylated liposomal is teratogenic and embryotoxic in rats, and embryotoxic and abortifacient in rabbits. In humans, Caelyx pegylated liposomal is suspected to cause fetal harm when administered during pregnancy.
	Genotoxicity	Although no studies have been conducted with Caelyx pegylated liposomal, doxorubicin HCl (the pharmacologically active ingredient of Caelyx pegylated liposomal) is known to be mutagenic and clastogenic (IARC 1987). Reported mutagenic activities of doxorubicin HCl include DNA damage induced in rabbit spermatozoa and dominant lethal mutations in mice. Like doxorubicin HCl, Caelyx pegylated liposomal may potentially induce chromosomal damage in human spermatozoa. Pegylated placebo liposomes are neither mutagenic nor genotoxic.
	Carcinogenicity	Although no studies have been conducted with Caelyx pegylated liposomal, doxorubicin HCl is mutagenic and carcinogenic (IARC 1987).
	Other toxicity studies (if applicable)	Local toxicity The results of local tolerance studies suggest that extravasated Caelyx pegylated liposomal may be less irritating than CD. A local tolerance study, performed in a non-rodent species receiving Caelyx by IV injection revealed no treatment-related injection-site intolerance. However, after subcutaneous administration, dose dependent inflammatory reactions have been observed indicating that Caelyx may provoke an inflammatory response after accidental perivenous administration (EMA 2019). Nephrotoxicity

Type of study		Key safety findings/Relevance to human usage
		A study has shown that Caelyx pegylated liposomal at a single IV dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Dermal toxicity After repeated administration of Caelyx pegylated liposomal to rats and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In a study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia, have also been observed in patients after long-term IV infusion.
Safety pharmacology	**Cardiovascular system (including potential effect on the QT interval)**	Studies in rabbits have shown that the cardiotoxicity of Caelyx pegylated liposomal is reduced compared with CD preparations. In a repeat-dose toxicity study, no pathology changes were seen in the heart of Wistar rats dosed with Caelyx pegylated liposomal at 2 mg/kg, once weekly for 7 weeks (EMA 2019).
	Nervous system	No specific safety pharmacology studies looking at the nervous system were performed.
	Immune system	Anaphylactoid response During repeat-dose toxicology studies in dogs, an acute response characterized by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with Caelyx pegylated liposomal and CD. The hypotensive response was reduced in magnitude by pre-treatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.
	Hemolytic potential	The hemolytic potential of Caelyx and placebo liposomes in human blood was assessed in vitro, as well as compatibility with human serum and plasma. Neither Caelyx nor the empty liposomes caused any hemolysis of human red blood cells or any coagulation or precipitation of human serum or plasma (EMA 2019).

Other toxicity-related information or data

Overall, the toxicity profile of Caelyx pegylated liposomal in animals is similar across species, and target organs of toxicity in animals have been predictive of human toxicity. Safety concerns relevant to use in humans include cardiotoxicity, myelosuppression, dermal toxicity (cutaneous lesions) and fetal toxicity. These risks are not included in the RMP as important safety concerns as they are considered fully characterized and appropriately managed with routine risk minimization measures in the product information which are part of standard clinical practice (see Part II, Module SVII).

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

Caelyx pegylated liposomal has been marketed since 17 NOV 1995. It was marketed initially by Schering-Plough Ltd (Kenilworth, New Jersey, United States) until January 2011 when Janssen-Cilag International, N.V. assumed all responsibilities for safety reporting, distribution, and marketing worldwide. The application for MA transfer to Baxter Holding B.V. in the EEA was approved on 20 AUG 2021.

The clinical development program included subjects exposed to Caelyx pegylated liposomal in studies conducted by previous MAHs and their partners. The drug product was clinically developed by Cilag GmbH (Janssen). Within the clinical development program, this compound had also a co-development partner, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Therefore, the presentation of the overall cumulative estimate of subjects in the compound development program is a best estimate based on the documentation received following MA transfer. An estimated 4,644 subjects were exposed to Caelyx pegylated liposomal during clinical development. There are no new data with regards to clinical trial exposure since the acquisition of this product by Baxter.

The calculation of cumulative exposure is limited by the unavailability of historical clinical trial data. Due to the age of the studies as well as the lack of availability of raw data through MA transfers, not all data could be integrated for stratification by duration, age/gender, dose or ethnicity. Some data regarding the demographics of clinical trial exposure was extracted from final clinical study reports (CSRs). The data from final CSRs and the integrated data are presented separately for clarity and transparency.

Of the 4,644 subjects exposed to Caelyx pegylated liposomal in the clinical development program, demographic data was not available for 325 subjects.

It is important to note this is the first update to the EU-RMP prepared by Baxter since version 5.0, submitted in October 2013 by Janssen-Cilag International NV. Therefore, the presentation and format of the data and text differ from the previous EU RMP due in part to the updated EMA template guidance as well as lack of availability of raw data. The tables below outline the information available for clinical trial exposure.

Estimated cumulative subject exposure from clinical trials (integrated data)	
Treatment	**Subjects**
Caelyx pegylated liposomal[a]	4,319[b]
Comparator	1,571[b]

Subtotal	5,890
Estimated cumulative subject exposure from clinical trials (non-integrated data)	
Treatment	**Subjects**
Caelyx pegylated liposomal[a]	325[c]
Comparator	116[c]
Subtotal	441
Caelyx pegylated liposomal total[abcd]	**4,644**
Comparator total[bcd]	**1,687**

[a] Includes subjects that received PLD as a single agent or in combination with other agents.

[b] Includes subjects from the following studies for which data is available: 30-22, 30-47, 30-47E, 30-49, 30-57, 30-45, 30-50, 30-42, 30-48, 30-65, I97-328, I96 352, DOXIL BCA-3001, C2000- 003, 30-03, 30-05, 30-12, 30-14, 30-24, 30-25, 30-26, 30-10, 30 1130-38, ECOG-E1D96, DOXILMMY-3001, DOXIL-NAP-1002, DOXIL NAP-1004.

[c] Includes subjects from the following studies for which data is not available: C2000-002, D004-23-006, DOXIL-MMY-2001, DOXILOVC2007, DOXILOVC3001, JNS002-JPN-01, JNS002-JPN-02, and JNS002-JPN-03.

[d] In the case that a subject participated in more than one study, the subject is counted once for each study

Total subjects included in clinical trials by indication (integrated data)[a]			
Indication	**Study**	**Total number of subjects[b]**	**Treatment regimen (Caelyx vs Comparator**
Ovarian cancer	30-22	35	Single agent Caelyx
	30-47	122	Single agent Caelyx
	30-47E	62	Single agent Caelyx
	30-49 (Gordon 2001, Gordon 2004)	474	Single agent Caelyx vs. topotecan
	30-57	216	Single agent Caelyx vs. Taxol
	DOXIL-NAP-1002[c]	53	Single agent Caelyx
	DOXIL-NAP-1004 [c]	35	Single agent Caelyx
Breast cancer	30-45	11	Single agent Caelyx
	30-50	37	Single agent Caelyx
	30-42	34	Single agent Caelyx vs. Taxol
	30-48	17	Single agent Caelyx vs. Taxotere
	30-65	25	Single agent Caelyx vs. Navelbine

Total subjects included in clinical trials by indication (integrated data)[a]			
Indication	**Study**	**Total number of subjects[b]**	**Treatment regimen (Caelyx vs Comparator**
	I97-328 (O'Brien 2004)	500	Single agent Caelyx vs. doxorubicin
	I96 352 (Keller 2004)	295	Single agent Caelyx vs. Navelbine vs. mitomycin C+vinblastine
	DOXIL BCA-3001	750	Caelyx+docetaxel vs. docetaxel
Multiple myeloma	C2000- 003-03 (Rifkin 2006)	192	vincristine/Caelyx/ dexamethasone vs. vincristine/doxorubicin/ dexamethasone
	DOXILMMY-3001 (Orlowski 2007, Orlowski 2016)	636	Caelyx+Velcade vs. Velcade
AIDS-related KS	30-03	250	Single agent Caelyx
	30-05	18	Single agent Caelyx
	30-12	892	Single agent Caelyx
	30-14	43	Single agent Caelyx
	30-24	94	Single agent Caelyx
	30-25	635	Single agent Caelyx
	30-26	67	Single agent Caelyx
	30-10 (Northfelt 1998)	133	Single agent Caelyx
	30-11 (Stewart 1998)	121	Single agent Caelyx
	30-38 (Cooley 2007)	60	Single agent Caelyx
	ECOG-E1D96	83	Single agent Caelyx vs. paclitaxel

[a] Table reflects the total number of subjects for which data is available (n=5,890) exposed to Caelyx pegylated liposomal or a comparator; information extracted from final CSRs.

[b] In the case that a subject participated in more than one study, the subject is counted once for each study.

[c] A bioequivalence study which includes subjects with other solid tumors, including breast cancer.

SIII.1 Duration of exposure

Clinical trial exposure stratified by duration of exposure is not available due to the age of the studies and lack of availability of raw data. There are no new data with regards to duration of exposure since the acquisition of this product by Baxter.

SIII.2 Age group and gender

Data regarding age group and gender are not available for 325 out of 4,644 subjects exposed to Caelyx pegylated liposomal in the clinical development program.

Subject exposure to Caelyx pegylated liposomal by age group and gender (integrated data)			
	Subjects[a]		
Age group	**Male**	**Female**	**Total**
≥ 18 - 54 years	2,315	713	3,031[b]
≥ 55 - 64 years	175	537	712
≥ 65 - 74 years	75	367	442
≥ 75 years	26	100	126
Missing	5	N/A	8[c]
Total	**2,596**	**1,717**	**4,319**

[a] Includes subjects from the following studies: 30-22, 30-47, 30-47E, 30-49, 30-57, 30-45, 30-50, 30-42, 30-48, 30-65, I97-328, I96-352, DOXIL BCA 3001, C2000-003, 30-03, 30 05, 30-12, 30-14, 30-24, 30-25, 30-26, 30-10, 30-11, 30-38, ECOG E1D96, DOXILMMY3001, NAP1002 and NAP1004.

[b] Three subjects have missing gender data.

[c] Three subjects have missing age and gender data.

SIII.3 Dose

Integrated data for clinical trial exposure stratified by dose is not available due to the age of the studies and lack of availability of raw data. Dosing varied, depending on study parameters as well as the subject's study drug tolerability. The table below presents the treatment and dosing regimens from individual CSRs.

Treatment and dosing regimen			
Indication	**Study**	**Treatment regimen (Caelyx vs Comparator**	**Dosing regimen**
Ovarian cancer	30-22	Single agent Caelyx	50 mg/m^2 every 3 weeks
	30-47	Single agent Caelyx	50 mg/m^2 every 4 weeks
	30-47E	Single agent Caelyx	50 mg/m^2 every 4 weeks
	30-49	Single agent Caelyx vs. topotecan	50 mg/m^2 every 4 weeks

Treatment and dosing regimen			
Indication	**Study**	**Treatment regimen (Caelyx vs Comparator**	**Dosing regimen**
	30-57	Single agent Caelyx vs. Taxol	50 mg/m^2 every 4 weeks
	DOXIL-NAP-1002	Single agent Caelyx	50 mg/m^2 every 4 weeks (2 cycles only)
	DOXIL-NAP-1004	Single agent Caelyx	50 mg/m^2 every 4 weeks (2 cycles only)
Breast cancer	30-45	Single agent Caelyx	50 mg/m^2 every 4 weeks
	30-50	Single agent Caelyx	50-60 mg/m^2 every 3-4 weeks
	30-42	Single agent Caelyx vs. Taxol	30, 40, 50mg/m2 every 4 weeks
	30-48	Single agent Caelyx vs. Taxotere	30-40 mg/m^2 every 3-4 weeks
	30-65	Single agent Caelyx vs. Navelbine	40 mg/m^2 , day 1 and day 15 every 3 weeks
	I97-328	Single agent Caelyx vs. doxorubicin	50 mg/m^2 every 4 weeks
	I96 352	Single agent Caelyx vs. Navelbine vs. mitomycin C+vinblastine	50 mg/m^2 every 4 weeks
	DOXIL BCA-3001	Caelyx+docetaxel vs. docetaxel	30 mg/m^2 every 3 weeks
Multiple myeloma	C2000- 003-03	vincristine/Caelyx/ dexamethasone vs. vincristine/doxorubicin/ dexamethasone	40 mg/m^2 every 4 weeks
	DOXILMMY-3001	Caelyx+Velcade vs. Velcade	30 mg/m^2 every 3 weeks
AIDS-related KS	30-03	Single agent Caelyx	10-40 mg/m^2 every 2 weeks
	30-05	Single agent Caelyx	10, 20,40 mg/m^2 (single dose)
	30-12	Single agent Caelyx	20 mg/m^2 every 3 weeks
	30-14	Single agent Caelyx	10, 20 mg/m^2 every 3 weeks

Treatment and dosing regimen			
Indication	**Study**	**Treatment regimen (Caelyx vs Comparator**	**Dosing regimen**
	30-24	Single agent Caelyx	20 mg/m^2 every 3 weeks
	30-25	Single agent Caelyx	20 mg/m^2 every 3 weeks
	30-26	Single agent Caelyx	20 mg/m^2 every 3 weeks
	30-10	Single agent Caelyx	20 mg/m^2 every 2 weeks
	30-11	Single agent Caelyx	20 mg/m^2 every 3 weeks
	30-38	Single agent Caelyx	20 mg/m^2 every 2 weeks
	ECOG-E1D96	Single agent Caelyx vs. paclitaxel	20 mg/m^2 every 3 weeks

SIII.4 Ethnic or racial origin

Data regarding ethnic or racial origin are not available for 325 out of 4,644 subjects exposed to Caelyx pegylated liposomal in the clinical development program.

Subject exposure to Caelyx pegylated liposomal by ethnic or racial origin (integrated data)	
Ethnic or racial origin	**Subjects[a]**
White	3,352
Black or African American	224
Asian	38
Hispanic or Latino	246
Other	29
Not Reported	430[b]
Total	**4,319**

[a] Includes subjects from the following studies: 30 22, 30 47, 30-47E, 30-49, 30-57, 30-45, 30-50, 30-42, 30-48, 30-65, I97-328, I96-352, DOXIL BCA 3001, C2000-003, 30-03, 30-05, 30-12, 30-14, 30-24, 30-25, 30-26, 30-10, 30 11, 30-38, ECOG E1D96, DOXILMMY-3001, NAP1002 and NAP1004. In the case that a subject participated in more than one study, the subject is counted once for each study.

Subject exposure to Caelyx pegylated liposomal by ethnic or racial origin (integrated data)	
Ethnic or racial origin	**Subjects[a]**

[b] Race is not reported for 415 subjects from study 30-25, five subjects from study NAP1002, three subjects from study 30-03, two subjects from study 30-26, one subject from study ECOG-E1D96, and four subjects from study NAP1004.

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Due to the age of studies, not all exclusion criteria were available or they were limited based on information presented in final CSRs. Additionally, the exclusion criteria were not applicable to all studies, as they differed depending on the indication and study parameters.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Exclusion criterion: Pregnant or breastfeeding (all studies)		
Reason for exclusion	**Is it included as missing information in the RMP? (Yes/No)**	**Rationale if not included as missing information**
Pregnant or breastfeeding individuals were excluded from the clinical development program to avoid harm to the subject. Caelyx pegylated liposomal is suspected to cause serious birth defects when administered during pregnancy. It is not known whether Caelyx pegylated liposomal is excreted in human milk. Because many medicinal products, including anthracyclines, are excreted in human milk, the potential for serious adverse reactions in nursing infants cannot be excluded.	No	Use of Caelyx pegylated liposomal during pregnancy and lactation is discussed in the SmPC. Due to the potential for serious adverse events, Caelyx pegylated liposomal should not be used during pregnancy unless clearly necessary. Warning language that mothers must discontinue nursing prior to beginning Caelyx pegylated liposomal treatment is also included in the SmPC. Additionally, as stated in the SmPC, women of child-bearing potential should use effective contraceptive measures while being treated with Caelyx pegylated liposomal and for eight months following completion of treatment. Men are recommended to use effective contraceptive measures and to not father a child while receiving Caelyx pegylated liposomal and for six months following completion of treatment.
Exclusion criterion: Hypersensitivity to doxorubicin HCl, other components of Caelyx pegylated liposomal, or history of hypersensitivity to other anthracyclines (all studies)		
Reason for exclusion	**Is it included as missing information in the RMP? (Yes/No)**	**Rationale if not included as missing information**
Individuals with known hypersensitivity to doxorubicin HCl, other components of Caelyx pegylated liposomal, or other	No	Hypersensitivity to the active substance, peanut or soya, or to any of the excipients

anthracyclines were excluded from the clinical development program to avoid harm to the subject.		of Caelyx pegylated liposomal is a labeled contraindication in the SmPC.
Exclusion criterion: Subjects treated with local therapy or systemic alfa-interferon (studies supporting AIDS-related KS indication)		
Reason for exclusion	**Is it included as missing information in the RMP? (Yes/No)**	**Rationale if not included as missing information**
Individuals treated with local therapy or system alfa-interferon for AIDS-related KS were excluded from the clinical development program to avoid harm to the subject. Local therapy (e.g., injection of vincristine into subcutaneous lesions) or systemic alfa-interferon plus Caelyx pegylated liposomal may cause increased toxicity.	No	Use of Caelyx pegylated liposomal in patients with AIDS-related KS that may be treated effectively with local therapy or systemic alfa-interferon is a labeled contraindication in the SmPC.
Exclusion criterion: Clinically significant cardiac disease or a history or cardiac impairment (all studies)		
Reason for exclusion	**Is it included as missing information in the RMP? (Yes/No)**	**Rationale if not included as missing information**
Individuals with clinically significant cardiac disease or a history of cardiac impairment were excluded from the clinical development program to avoid harm to the subject. Cardiac toxicity is known side effect of anthracycline treatment.	No	Baxter does not anticipate the safety profile to differ from that characterized so far in this patient population, if appropriately managed. The SmPC contains warning language regarding cardiac toxicity with use of this product. Additionally, clinical guidance on use of Caelyx pegylated liposomal in patients with cardiac disease requiring treatment is provided. The prescribing clinician must consider the benefits and risks of using Caelyx pegylated liposomal in each individual patient.
Exclusion criterion: Patients with other clinically significant conditions including: • **Malignant disease (except basal or squamous cell carcinoma or carcinoma in situ of the cervix) within five years of randomization (studies supporting breast cancer indication)** • **Abnormal hematological parameters: platelets <100,000, ANC <1,500, or hemoglobin <9 g/dl (studies supporting breast cancer indication)**		

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- **Abnormal renal function: creatinine greater than 1.5 x upper limit of normal range (studies supporting breast cancer indication) or clinically significant kidney disease (studies supporting AIDS-related KS and multiple myeloma indications)**
- **Abnormal liver function (studies supporting breast cancer indication) or clinically significant liver disease (studies supporting AIDS-related KS and multiple myeloma indications)**
- **Uncontrolled systemic infection (studies supporting multiple myeloma, breast cancer and ovarian cancer indications)**
- **Uncontrolled diabetes (studies supporting multiple myeloma indication)**
- **Patients with central nervous system involvement (studies supporting multiple myeloma, breast cancer and ovarian cancer indications)**
- **Peripheral neuropathy of Grade 2 or higher severity as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (studies supporting multiple myeloma indication)**
- **Active opportunistic infection with mycobacteria, cytomegalovirus, toxoplasmosis, P. carinii or other microorganism if under treatment with myelotoxic drugs (studies supporting AIDS-related KS indication)**

</td></tr>
<tr><th>Reason for exclusion</th><th>Is it included as missing information in the RMP? (Yes/No)</th><th>Rationale if not included as missing information</th></tr>
<tr><td>Patients with the above clinically significant conditions were excluded from the clinical trial development program (as described) to prevent further harm to the subject. Treatment with Caelyx pegylated liposomal could worsen the described conditions. Additionally, the above-described conditions may confound the assessment of Caelyx-emergent adverse events, and potentially interfere with interpretation of study results.</td><td>No</td><td>Baxter does not anticipate the safety profile to differ from that characterized so far in this patient population, if appropriately managed. Use of Caelyx pegylated liposomal in patients with pre-existing disease including diabetic patients, patients with AIDS, and patients with hepatic or renal impairment is described in the SmPC. The prescribing clinician must consider the benefits and risks of using Caelyx pegylated liposomal in each individual patient.</td></tr>
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Exclusion criterion: Concomitant treatments including the following:

- **Treatment with radiation or electron beam therapy within the preceding 3 weeks (studies supporting AIDS-related KS indication)**
- **Prior radiotherapy to an area greater than one-third of the skeleton or prior local radiotherapy within 1 week of treatment (studies supporting multiple myeloma indication)**
- **Radiation to disease areas within 3 weeks of study treatment initiation (studies supporting breast cancer indication)**
- **Prior mediastinal or whole pelvic radiation (studies supporting ovarian cancer indication)**

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• **Prior neoplasms treated with extensive chemotherapy, which in the investigator's opinion had led to an irreversible compromise of bone marrow function (studies supporting AIDS-related KS indication)** • **Prior chemotherapy within 28 days of first dose of Doxil (studies supporting breast cancer and ovarian cancer indications) or prior chemotherapy to treat multiple myeloma** • **Prior single-agent dexamethasone (or another corticosteroid) to treat multiple myeloma** • **Treatment with strong CYP3A4 inhibitors or strong CYP3A4 inducers from at least 4 weeks before the first dose of Caelyx pegylated liposomal (all studies)**		
Reason for exclusion	**Is it included as missing information in the RMP? (Yes/No)**	**Rationale if not included as missing information**
Individuals who had the concomitant treatments described above were excluded from the clinical development program to avoid harm to the subject as well as prevent interference with interpretation of study results. Doxorubicin HCl preparations may potentiate the toxicity of other anti-cancer therapies (e.g., increased risk of cardiac toxicity in patients with prior mediastinal irradiation or those receiving concurrent cyclophosphamide therapy). Prior radiotherapy may also result in radiation recall phenomenon upon Caelyx pegylated liposomal administration. Further, subjects with these treatments may require a Caelyx pegylated liposomal dose and monitoring different than what was used during the study.	No	Baxter does not anticipate the safety profile to differ from that characterized so far in this patient population, if appropriately managed. The SmPC provides dose modifications and warning language regarding concomitant use of medicinal products known to interact with standard doxorubicin HCl. The prescribing clinician must consider the benefits and risks of using Caelyx pegylated liposomal in each individual patient.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

With an overall exposure of an estimated 4,644 subjects, and varying study parameters (e.g., duration of exposure, follow-up after study drug exposure) the clinical development program is unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Though there were limitations in the clinical trial development program, it is important to note that the safety profile of Caelyx pegylated liposomal has been established with over two decades of post-marketing use. The SmPC provides warning language regarding adverse reactions that occur with prolonged and cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Exposure of special populations included in clinical trial development program(s) are presented in the table below.

Type of special population	Exposure
Pregnant women	Not included in the clinical trial development program.
Breastfeeding women	Not included in the clinical trial development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with clinically significant cardiac, hepatic and renal disease were not included in the clinical trial development program. The medical histories (level of hepatic impairment, renal impairment and immune status) of the 4,644 subjects exposed to Caelyx pegylated liposomal in the clinical development program varied. In general, many patients treated with Caelyx pegylated liposomal had co-morbidities due to their disease state or baseline myelosuppression (due to factors such as pre-existing HIV disease, numerous concomitant or previous medications, or tumors involving bone marrow). Caelyx pegylated liposomal is used for treatment of multiple conditions and therapy is titrated to effect, so different disease severity is accounted for in product dosing.
Population(s) with relevant different ethnic origin	Racial or ethnic origin was not collected from all clinical trials. Of the subjects for which data was collected, 77% were White, 5% were Black or African-American, 6% were Hispanic/Latino, and 2% were of other racial background. No race-based efficacy evaluation was performed across subjects for whom race was known.
Subpopulations carrying relevant genetic polymorphisms	In study DOXIL-BCA-3001, a pharmacogenomic analysis was done on subjects with advanced breast cancer. The purpose of the pharmacogenomic analysis was to test whether polymorphisms (i.e., g.4812A>C,M35T, H63C, S65C, E168Q, and C282Y) in the hemochromatosis gene are associated with increased susceptibility to doxorubicin-induced cardiac toxicity when receiving Caelyx pegylated liposomal+docetaxel (n=207) vs. docetaxel monotherapy only (n=219). No significant association ($p < 0.05$) with any of the genotypes tested was found.

PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

The tables below detail post-authorization use based on unit sales of Caelyx pegylated liposomal. Baxter does not capture detailed demographic data (indication, age, gender, race, ethnicity, and medical history) on patients in the EU who were administered Caelyx pegylated liposomal therapy. Therefore, the presentation of the post-authorization experience differs from the previous EU RMP (version 5.0 prepared by the previous MAH).

SV.1.1 Method used to calculate exposure

Due to the large number of parameters taken into account to calculate the patient exposure, the number of vials sold worldwide, which indirectly reflects the patient exposure, is provided.

SV.1.2 Exposure

Cumulative exposure

The total number of vials of Caelyx pegylated liposomal sold from product launch to 30 APR 2023 was 10,502,877.

Estimated exposure by indication

Estimated exposure by indication is not available for Caelyx pegylated liposomal.

Estimated exposure by age and gender

Estimated exposure by age and gender is not available for Caelyx pegylated liposomal.

Estimated exposure by route

Not applicable; Caelyx is indicated only for IV infusion.

Estimated exposure by formulation

Not applicable; Caelyx is available in a single formulation, i.e., 2 mg/mL concentrate for solution for infusion.

Estimated exposure by region

Region	Proportional sales[a] by region	Total vials sold by region
Europe	[redacted]	[redacted]

Region	Proportional sales[a] by region	Total vials sold by region
North America	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]
Totals	[redacted]	[redacted]

[redacted]

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for misuse of Caelyx pegylated liposomal for illegal purposes is considered unlikely and has not been reported.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The initial RMP was prepared by Schering-Plough; the approval date is unavailable. The following safety concerns were included in the initial RMP (version 1.0 issued 01 JUN 2007):

Important Potential Risks

- Cardiotoxicity
- Renal Failure
- Interstitial Lung Disease

SVII.2 New safety concerns and reclassification with submission of an updated RMP

There are no safety concerns included in this RMP; previous safety concerns included in version 5.0 of the EU RMP (issued 16 SEP 2013) have been reclassified based on EMA GVP Module V Revision 2 guidelines.

The following have been removed as important identified risks and important potential risks with this RMP update, as they are known risks that require no further characterization and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice):

Important identified risks:

- Cardiotoxicity
- Cutaneous Lesions
- Secondary Oral Neoplasms
- Myelosuppression

Important potential risk:

- Interstitial Lung Disease

The following have been removed as important potential risks with this RMP update they are known potential risks that are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are sufficient to minimize the risk:

- Renal Failure
- Foetal Toxicity

Use in Paediatric Patients has been removed from the list of safety concerns as an item of missing information as the safety profile is not expected to differ from that characterized so far in this patient population. Use of Caelyx pegylated liposomal is not recommended in patients below 18 years of age. However, limited Phase I safety data indicate that doses up to 60 mg/m^2 every 4 weeks are well tolerated in pediatric patients, though effectiveness in patients under 18 years of age has not been established.

SVII.3 Details of important identified risks, important potential risks, and missing information

Not applicable; there are no safety concerns included in this RMP.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

There are no safety concerns included in this RMP. All risks associated with the use of Caelyx pegylated liposomal are considered fully characterized in the product information. All such risks are subject to routine pharmacovigilance monitoring through standard adverse reaction reporting and routine signal detection activities.

Adverse reaction follow-up questionnaires

Not applicable.

Other forms of routine pharmacovigilance, beyond adverse reaction reporting and routine signal detection

Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned post-authorization efficacy studies which have been imposed as a condition of the marketing authorization or as a specific obligation.

PART V: RISK MINIMIZATION MEASURES

V.1 Routine risk minimization measures

There are no safety concerns included in this RMP. All risks associated with the use of Caelyx pegylated liposomal are considered fully characterized and appropriately managed with routine risk minimization measures in the product information which are part of standard clinical practice.

V.2 Additional risk minimization measures

Not applicable.

V.2.1 Removal of additional risk minimization measures

Not applicable.

V.3 Summary of risk minimization measures and pharmacovigilance activities

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion (pegylated liposomal doxorubicin hydrochloride)

This is a summary of the Risk Management Plan (RMP) for Caelyx pegylated liposomal 2 mg/ml concentrate for solution for infusion (hereafter Caelyx pegylated liposomal). The RMP provides details on the important risks of Caelyx pegylated liposomal, how these risks can be minimized, and how more information will be obtained about the important risks.

The Summary of Product Characteristics (SmPC) and Package Leaflet (PL) for Caelyx pegylated liposomal provide essential information to healthcare professionals and patients on how Caelyx pegylated liposomal should be used.

This summary of the RMP for Caelyx pegylated liposomal should be read in the context of all other related information, including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

New safety concerns and/or changes to the current safety concerns will be included in future updates of the RMP.

I. The medicine and what it is used for

Caelyx pegylated liposomal is authorized for monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk, for treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen, in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant, and for treatment of acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) in patients with low Cluster of Differentiation 4 (CD4) counts (< 200 CD4 lymphocytes/mm3) and extensive mucocutaneous or visceral disease; refer to the SmPC for complete indication wording. It contains pegylated liposomal doxorubicin hydrochloride as the active substance, and it is given intravenously.

Further information about the evaluation of Caelyx pegylated liposomal's benefits can be found in the EPAR, including in its plain-language summary, available on the EMA website under the medicine's webpage: <>.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

There are no important risks included in the RMP for Caelyx pegylated liposomal; however, measures to minimize the risks for any medicinal products may be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription).

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of medicinal products are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of medicinal products. Potential risks are concerns for which an association with the use of the medicinal product is possible based on available data, but this association has not been established yet and needs to be further monitored. Missing information refers to information on the safety of the medicinal product that is currently missing and further information may need to be collected (e.g., on the long-term use of the medicine).

There are no important risks or missing information included in the RMP for Caelyx pegylated liposomal.

List of important risks and missing information	
Important identified risks	None
Important potential risks	None

List of important risks and missing information	
Missing information	None

II.B Summary of important risks and missing information

There are no important risks or missing information included in this RMP. All risks associated with the use of Caelyx pegylated liposomal are considered fully characterized and appropriately managed with routine risk minimization measures in the product information which are fully integrated into standard clinical practice.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligations of Caelyx pegylated liposomal.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Caelyx pegylated liposomal.

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6: Details of additional risk minimization measures

Not applicable.