אוקטובר 2022

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הריני להודיעכם כי העלון לרופא של התכשיר עודכן:

ויקסאוס ליפוזומל **VYXEOS LIPOSOMAL**

POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

מרכיבים פעילים :
cytarabine
daunorubicin (as HCL)

התוויה מאושרת :

Vyxeos liposomal is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

להלן העדכונים בעלון לרופא המהווים החמרות:

4.2 Posology and method of administration
[…]

Posology
Vyxeos liposomal dosing is based on the patient's body surface area (BSA) according to the following schedule:

Table 1: Dose and ~~ing~~ schedule for Vyxeos liposomal
[…]

Special populations

Renal impairment

Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]), ~~or~~ moderate (CrCL 30 mL/min to 59 mL/min) or severe (CrCL<30 mL/min) renal impairment. There is no experience with Vyxeos liposomal in patients with ~~severe renal impairment (CrCL 15 mL/min to 29 mL/min) or~~ end-stage renal disease managed with dialysis. ~~Vyxeos liposomal should only be used inpatients with severe renal impairment if the benefits outweigh the risks~~ (See sections ~~4.4 and~~ 5.2).
[…]

Paediatric population

Outside its authorised indications Vyxeos liposomal has been studied in paediatric and young adult patients aged 1-21 years with relapsed AML. Due to the limited size of these trials, it is not possible to conclude that the benefits of the use outweigh the risks.

Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made ~~The safety and efficacy of Vyxeos liposomal in children aged 0-18 years have not yet beenestablished. No data are available.~~
[…]

4.4 Special warnings and precautions for use
[…]

Cardiotoxicity
[…]

In two single arm studies of 65 anthracycline pre-treated children with relapsed or refractory AML treated with a single induction cycle (Cycle 1) of Vyxeos liposomal, cardiac disorders (including sinus tachycardia, QT prolongation and ejection fraction decreased) were observed. Several other long-term studies of treatment with anthracycline/ anthracenedione in children suggest that congestive cardiomyopathies with a latency of many years may occur (see section 4.8)
[…]

Evaluation of hepatic and renal function
Hepatic ~~or renal~~ impairment may increase the risk of toxicity associated with daunorubicin and cytarabine. Evaluation of hepatic ~~and renal~~ function using conventional clinical laboratory tests is recommended prior to administration of Vyxeos liposomal and periodically during treatment. There is no experience with Vyxeos liposomal in patients with baseline serum bilirubin greater than 50 µmol/L, ~~severe renal impairment (creatinine clearance less than 30 mL/min),~~ or end~~-~~-stage renal disease managed with dialysis. Vyxeos liposomal should only be used in patients with severe hepatic ~~and/or renal~~ impairment if the benefits outweigh the risks (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Vyxeos liposomal. The delivery of daunorubicin and cytarabine in the Vyxeos liposomal formulation is anticipated to reduce the possibility of interactions, because systemic free ~~drug~~ concentrations of daunorubicin and cytarabine are much lower than when administered as the non-liposomal formulation.

4.6 Fertility, pregnancy and lactation
[…]

Breast-feeding
It is not known whether Vyxeos liposomal is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding children from Vyxeos liposomal, mothers should be advised not to ~~discontinue~~ breast-feed~~ing~~ during Vyxeos liposomal therapy.

4.8 Undesirable effects
[…]

Haemorrhage
Due to the thrombocytopenia experienced with Vyxeos liposomal a variety of haemorrhagic events were seen in clinical studies. The most common haemorrhagic event was epistaxis, and the majority of these were considered not serious (29.1%). The incidence of haemorrhage events is 69.1%; the incidence of non-serious events of haemorrhage was 67.2 %; the incidence of serious events of haemorrhage is 5.6%; the incidence of haemorrhage which led to discontinuation is 0. The incidence of fatal haemorrhage was 2.1%. Serious or fatal haemorrhagic events, including fatal ~~central nervous system (~~CNS~~)~~ haemorrhages, associated with severe thrombocytopenia were seen in patients treated with Vyxeos liposomal (see section 4.4).
[…]

Paediatric population
The safety profile of Vyxeos liposomal in 38 paediatric patients with relapsed AML in study AAML1421 appeared to be in general similar to that observed in the approved indication in adults with newly treated AML treated with Vyxeos liposomal (see section 4.2). However, adverse events in study AAML 1421 observed in paediatric patients that were different from or more severe than those seen in adults (acknowledging limitations of cross study comparisons) included rash maculo-papular (47.4%), electrocardiogram QT prolongation (28.9%), the early onset of cardiotoxicity (defined as > 10% decrease LVEF to final LVEF < 50% LVEF; 21.0%), severe hypokalaemia (13.2%), hyperglycaemia (7.9%) and ALT increased (7.9%). Hypertension was observed in 18.2% of these paediatric patients.

No paediatric long-term safety data beyond the study duration (26 months) are available. There is, thus, no paediatric safety data to address the long-term cardiotoxicity of Vyxeos liposomal, including long-term cardiotoxicity when used at doses above the maximum life-time cumulative anthracycline dose. There are no data on the effects of Vyxeos liposomal treatment on growth and maturation

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, combinations of antineoplastic agents, cytarabine and daunorubicin, ATCcode: L01XY01.

[…]

Clinical efficacy and safety

The efficacy of Vyxeos liposomal in adults for the treatment of newly diagnosed AML was evaluatedin a single ~~one~~ controlled clinical study (Study 301) and the efficacy of Vyxeos liposomal in paediatric patients for the treatment of relapsed AML was evaluated in a single clinical study AAML 1421.

[…]

Paediatric population

Relapsed AML

The efficacy of Vyxeos liposomal as a single agent was evaluated in a phase 1/2, single-arm study (AAML 1421) conducted to evaluate safety and efficacy of Vyxeos liposomal in 38 paediatric and young adult patients aged 1-21 years with AML in first relapse. Study treatment consisted of one induction cycle of Vyxeos liposomal 59 mg/135 mg/m2 administered intravenously over 90 minutes on Days 1, 3, and 5 followed by Fludarabine, Cytarabine, and G-CSF (FLAG) for cycle 2. The median age of patients was 11 years (range, 1-21 years). Eight (21%) of the patients were between 18 and 21 years; patients who received > 450 mg/m2 daunorubicin equivalents were excluded from the study.

The primary endpoint was overall response rate (defined as CR or CRp) after Vyxeos liposomal (Cycle 1) followed by FLAG (Cycle 2). The overall response rate was 68 (90% Clopper-Pearson CI 53% to 80%). After cycle 1, 16 (43%) patients had a treatment response of CR + CRp, including 14 (38%) patients who achieved CR, and based on the 7 subjects with relapse data available the median duration of CR was 284 days

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Vyxeos liposomal in one or more subsets of the paediatric population in AML (see section 4.2 for information on paediatric use).~~

5.2 Pharmacokinetic properties

[…]

Special populations

In a population pharmacokinetic analysis, no clinically meaningful effects on clearance and volume parameters of daunorubicin and cytarabine by age (1 to 81 years),~~Age~~, sex, race, body weight, body mass index, and white blood cell count were observed.~~do not have a clinicallyimportant effect on the exposure of total daunorubicin or cytarabine after adjusting dose by body surface area.~~

Paediatric population

The dose-normalized mean exposures of total daunorubicin and cytarabine observed in paediatric patients after 59 mg/135 mg/m^2 were comparable to those of daunorubicin and cytarabine after 44 mg/100 mg/m^2 in adults~~Insufficient pharmacokinetic data were collected in paediatric patients to draw conclusions.~~

[…]

Renal impairment

Based on a dedicated study to evaluate the impact of moderate to severe renal impairment on the pharmacokinetics of Vyxeos liposomal and a population pharmacokinetic analysis using data from clinical studies in patients with mild to moderate renal impairment, no significant difference in clearance of daunorubicin or cytarabine was observed in patients with pre-existing mild, moderate or severe renal impairment compared to patients with baseline normal renal function. The potential effects of end-stage renal disease managed with dialysis on the pharmacokinetics of daunorubicin and cytarabine administered as Vyxeos liposomal are unknown(see section 4.2).

Hepatic impairment

The pharmacokinetics of total daunorubicin and cytarabine were not altered in patients with bilirubin ≤ 50 µmol/L. The pharmacokinetics in patients with bilirubin greater than 50 µmol/L is unknown.

~~*Renal impairment*~~

~~Based on a dedicated study to evaluate the impact of moderate to severe renal impairment on the pharmacokinetics of Vyxeos liposomal and a population pharmacokinetic analysis using data from clinical studies in patients with mild to moderate renal impairment, , no significant difference in clearance of daunorubicin or cytarabine was observed in patients with pre-existing mild, to moderate or severe renal impairment (60 mL/min ≥ to ≤ 89 mL/min creatinine clearance [CrCL] for mild, and 30 mL/min ≥ to ≤ 59 mL/min creatinine clearance [CrCL] for moderate) compared to patients with baseline normal renal function (CrCL ≥ 90 mL/min). The potential effects of severe renal impairment (CrCL 15 mL/min ≥ to ≤ 29 mL/min, C-G) and end-stage renal disease managed with dialysis on the pharmacokinetics of daunorubicin and cytarabine administered as Vyxeos liposomal are unknown(see section 4.2).~~

5.3 Preclinical safety data

The ~~R~~repeat-dose toxicity of Vyxeos liposomal was tested in two-cycle intravenous infusion toxicity studies with 28-day recovery periods ~~conducted~~ in rats and dogs. Adverse effects of Vyxeos liposomal occurred at all ~~tested~~ dose levels (low to ~~null~~ no safety margins b~~as b~~ased on systemic exposures) and were generally consistent with those ~~known~~ documented for non-liposomal daunorubicin and/or cytarabine, comprising mainly ~~findings of~~ gastrointestinal and hematological ~~toxicity~~findings. Although central nervous system (CNS) ~~)~~and cardiovascular system safety parameters were included in these studies, given the observed morbidity and mortality, there was insufficient information to conduct ~~arrive at~~ an integrated assessment of the safety pharmacology of Vyxeos liposomal. ~~Vyxeos liposomal contains daunorubicin, which is known for its profound cardiotoxicity potential, and cytarabine, which is known to be associated with CNS toxicities.~~

Genotoxicity, ~~C~~carcinogenicity ~~, mutagenicity,~~ and reproductive and developmental toxicity studies have not been conducted with Vyxeos liposomal. However, studies are available with the single agents.

Genotoxicity

Cytarabine or its active metabolite Ara-C was mutagenic (bacterial mutagenicity assay) and ~~-~~clastogenic *in vitro* (chromosome aberrations and sister-chromatid exchanges (SCE) in human leukocytes) and *in vivo* (chromosome aberrations and SCE assay in rodent). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells *in vitro* and was clastogenic to meiotic cells. Daunorubicin was mutagenic (bacterial mutagenicity assay, V79 hamster cell assay) and clastogenic in vitro (CCRF CEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow).

Carcinogenicity
Studies with cytarabine were not identified. Published data with Ara-C, the active metabolite of cytarabine, did not provide evidence of carcinogenicity. Published data with daunorubicin suggest possible tumorigenicity in rats after a single dose~~s~~ of 5 or 10 mg/kg (0.68 to 1.4 times the RHD based on mg/m^2). The IARC Working Group (IARC 2000) classified daunorubicin in Group 2B (possibly carcinogenic to humans).

~~While cytarabine is not a carcinogen, daunorubicin is a possible carcinogen, hence, Vyxeos liposomal may be associated with a carcinogenic potential. Both daunorubicin and cytarabine are genotoxic, therefore, Vyxeos liposomal may be associated with a genotoxic risk.~~

~~A high incidence of mammary tumours was observed about 120 days after a single intravenous dose of daunorubicin in rats (at about 1.7 times the human dose on a mg/m^2 basis). Daunorubicin was mutagenic in *in vitro* tests (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRF-CEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests.~~

~~Cytarabine was mutagenic in *in vitro* tests and was clastogenic *in vitro* (chromosome aberrations and SCE in human leukocytes) and *in vivo* (chromosome aberrations and SCE assay in rodent bone~~

~~marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cellsand rat H43 cells *in vitro*.~~

~~Cytarabine was clastogenic to meiotic cells.~~

Reproductive and developmental toxicity
~~Both c~~Cytarabine ~~and daunorubicin, tested separately,~~was ~~showed teratogenic and~~ embryotoxic in mice and teratogenic in mice and rats~~effects in animal studies.~~ when administered during organogenesis. Cytarabine also caused, sperm-head abnormalities in mice and impaired spermatogenesis in rats. A single dose of cytarabine in rats, administered on day 14 of gestation, reduced prenatal and postnatal brain size and caused permanent impairment of learning ability. Daunorubicin was embryotoxic and caused fetal malformations when given during the period of organogenesis in rats. ~~Furthermore, daunorubicin~~ Daunorubicin caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules in dogs~~ and cytarabine, sperm-head abnormalities in mice. A single dose ofcytarabine in rats, administered on day 14 of gestation, reduced prenatal and postnatal brain size and caused permanent impairment of learning ability~~.

העלון לרופא נמצא בקישור, וכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

בברכה,

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