Gazyva®

Obinutuzumab

Composition

Active substance: Obinutuzumab
Excipients: L-histidine/L-histidine hydrochloride, trehalose, poloxamer 188, water for injection.

Pharmaceutical form and quantity of active substance per unit

Concentrate for solution for infusion.

Each 40 ml vial contains 1000 mg obinutuzumab.

Indications and potential uses

Gazyvaro in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) and additional comorbidities.

Dosage and administration

Usual dosage

Treatment with Gazyvaro should only be conducted under the supervision of a medical specialist experienced in the management of cancer patients. The infusion should only be administered in a place where full resuscitation facilities are immediately available and under the close supervision of an experienced physician.

Prophylaxis of tumour lysis syndrome: Adequate hydration and administration of uricostatics (e.g. allopurinol) starting 12-24 hours before the start of the first Gazyvaro infusion are recommended for patients with a circulating lymphocyte count >25 × 109/l to reduce the risk of tumour lysis syndrome (see Warnings and precautions).

To prevent infusion reactions, premedication with an analgesic/antipyretic (e.g. paracetamol) and an antihistamine (e.g. diphenhydramine) should be given 30 to 60 minutes before every Gazyvaro infusion. In addition, intravenous glucocorticoids (100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone) should be given at least one hour before the start of the Gazyvaro infusion to all patients in the first cycle (days 1 and 2) and, in subsequent cycles, to those who have experienced a grade 3 infusion reaction during the previous infusion or with a lymphocyte count >25 × 109/l prior to the next treatment. Hypotension may occur as a feature of infusion reactions during Gazyvaro intravenous infusions. Therefore, interruption of antihypertensive treatments should be considered for 12 hours before, during and for the first hour after each Gazyvaro infusion.

Gazyvaro is administered as an intravenous infusion through a dedicated line and must not be given as an intravenous push or bolus infusion. Isotonic 0.9% sodium chloride solution should be used to prepare the infusion solution. At the start of treatment (first

infusion) the total dose should be distributed to two infusion bags (bag 1 with 100 mg and bag 2 with 900 mg) (see Additional information, Instructions for handling and disposal).

The recommended dosage of Gazyvaro is 1000 mg administered 3 times in the first cycle and once in each of cycles 2-6 (28-day cycles).

First infusion: The first infusion is administered at a rate of 25 mg/h over 4 hours (bag 1 with 100 mg). If this has been well tolerated, the second bag (bag 2 with 900 mg) can be infused at a rate of 50 mg/h, provided that sufficient time, appropriate conditions and medical supervision are available during the infusion. After the first 60 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. If an infusion reaction has occurred during the first 100 mg (see Table 1 for procedure), the second bag must be administered the following day. Patients developing respiratory symptoms or hypotension should be monitored for 24 hours.

Subsequent infusions (cycle 1 days 8 and 15 and cycles 2-6): Subsequent Gazyvaro infusions can be started at a rate of 100 mg/h, which can then be increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Table 1 Infusion rate modification guidelines for infusion reactions

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Once symptoms resolve, the infusion can be resumed at no more than half the previous rate (at time of infusion reaction). If no further infusion reaction symptoms occur, infusion rate escalation may resume. The first infusion (day 1) may be increased back up to 25 mg/h after 1 hour, but not increased further. If a second grade 3 infusion reaction occurs, treatment with Gazyvaro should be discontinued.
Grades 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Once symptoms resolve, continue infusion. If no further infusion reaction symptoms occur, the infusion rate may be escalated at the increments and intervals appropriate to the treatment dose (see *Subsequent infusions* above). The first infusion on day 1 may be increased back up to 25 mg/h after 1 hour, but not increased further.

Delayed or missed doses

If a planned dose of Gazyvaro is missed, it should be administered as soon as possible, without waiting until the next planned dose. The planned treatment interval (e.g. 28 days) for Gazyvaro should be maintained between doses.

Dosage modifications during treatment

Dose reduction of Gazyvaro is not recommended.

Special dosage instructions

Elderly patients

No dose adjustment is required for patients in this age group.

Children and adolescents

No safety and efficacy studies have been conducted in children and adolescents under 18 years of age.

Renal impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) >30 ml/min. Gazyvaro has not been studied in patients with CrCl ≤30 ml/min.

Hepatic impairment

The safety and efficacy of Gazyvaro have not been studied in patients with hepatic impairment.

Contraindications

Known (IgE-mediated) hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

In order to improve the traceability of biological medicinal products, the tradename Gazyvaro should be clearly recorded in the patient's file. Replacement by another biological medicinal product requires the consent of the prescribing physician. Data in this prescribing information relate only to Gazyvaro.

Infusion reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyvaro were infusion reactions, which occurred predominantly during infusion of the first 1000 mg. The measures for preventing infusion reactions described under Dosage and administration decreased the incidence of all-grade infusion reactions. However, the incidences of grade 3 4 infusion reactions were similarly frequent with and without these measures. Most patients had no infusion reactions during subsequent infusions of Gazyvaro.

In the majority of patients, infusion reactions were mild to moderate and could be managed by slowing or temporarily halting the first infusion, but severe and life-threatening infusion reactions requiring symptomatic treatment have also been reported. Patients with a high tumour burden (lymphocytes >25 × 109/l) may be at increased risk of severe infusion reactions. See Dosage and administration for information on prophylaxis.

If the patient experiences an infusion reaction, the infusion should be managed according to the grade of the reaction. For a grade 4 infusion reaction, the infusion should be stopped and permanently discontinued. For a grade 3 infusion reaction, the infusion

should be temporarily interrupted and appropriate medication administered to treat the symptoms. For a grade 1-2 infusion reaction, the infusion should be slowed down and symptoms treated as appropriate. Once symptoms have resolved, the infusion can be resumed, except following a grade 4 infusion reaction, at no more than half the previous rate. If the patient does not experience the same adverse reaction with the same severity, the infusion rate may be escalated at the increments and intervals appropriate to the treatment dose. If the previous infusion rate was not well tolerated, the instructions for the cycle 1 day 1 and day 2 infusion rate should be followed (see Dosage and administration).

Patients experiencing any of the following events should not receive further Gazyvaro infusions:

- Acute life-threatening respiratory symptoms;
- A grade 4 (i.e. life threatening) infusion reaction, or
- A second (prolonged/recurrent) grade 3 infusion reaction (after resuming the first infusion or during a subsequent infusion).

Patients with pre-existing cardiac or pulmonary conditions should be carefully monitored during and after the infusion. Hypotension may be expected to occur during Gazyvaro infusions. Therefore, discontinuation of antihypertensive medications should be considered for 12 hours before, during and for the first hour after each Gazyvaro infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of discontinuing their antihypertensive medication.

Hypersensitivity reactions including anaphylaxis

Hypersensitivity reactions may be difficult to distinguish from infusion reactions. Anaphylaxis has been reported in patients treated with Gazyvaro. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be halted and permanently discontinued. Patients with known IgE-mediated hypersensitivity to Gazyvaro should not be treated with Gazyvaro (see *Contraindications*).

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS) have been reported during treatment with Gazyvaro. Patients assumed to be at risk of TLS (e.g. patients with a high tumour burden or a high circulating lymphocyte count [>25 × 109/l]) should receive appropriate tumour lysis prophylaxis with uricostatics (e.g. allopurinol) and hydration starting 12-24 hours before infusion of Gazyvaro, as described under Dosage and administration. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and initiate supportive measures, including dialysis, as indicated.

Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with Gazyvaro. Patients who experience neutropenia should be closely

monitored with laboratory tests until resolution. If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony-stimulating factors should be considered. Any signs of concomitant infection should be treated as appropriate. Cases of late-onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have been reported.

Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with Gazyvaro.

Fatal hemorrhagic events have also occurred in cycle 1 during treatment with Gazyvaro.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. The benefit-risk balance of all concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be carefully considered, especially during the first cycle.

Worsening of pre-existing cardiac conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred during treatment with Gazyvaro. These events may occur as part of an infusion reaction and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent potential fluid overload.

Infections

Gazyvaro should not be administered in the presence of an active infection. Caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Serious bacterial, fungal and new or reactivated viral infections can occur during and following the completion of Gazyvaro therapy. Fatal infections have been reported.

Patients with severe viral infections should not be treated with Gazyvaro. Severe viral infections, both new and reactivated or exacerbated, have been reported on treatment with anti-CD20 antibodies and have been fatal in isolated cases. Examples of such severe viral infections include infections with herpesviruses (cytomegaly, herpes zoster, herpes simplex), JC virus (progressive multifocal leukoencephalopathy [PML]) and hepatitis B or hepatitis C virus.

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyvaro (see Undesirable effects). HBV screening should be performed in all patients before initiation of treatment with Gazyvaro. At minimum this should include determination of HBsAg and anti-HBc, which can be complemented with other markers. Patients with active hepatitis B should not be treated with Gazyvaro. Patients with positive hepatitis B serology should consult a hepatologist before starting treatment. HBV reactivation has been reported in hepatitis B surface antigen-positive (HBsAg-positive) patients, as well as in HBsAg-negative and anti-HBs-positive patients.

Patients with existing or previous HBV infection should be observed for clinical symptoms or laboratory findings indicative of hepatitis or HBV reactivation during and for at least 12 months after treatment with Gazyvaro. Gazyvaro must be discontinued immediately in the event of hepatitis B reactivation. Resumption of treatment should be discussed with a physician experienced in the treatment of hepatitis B. No data are available on the safety of treatment resumption with Gazyvaro in patients with reactivated hepatitis B.

Progressive multifocal leukoencephalopathy (PML)

Cases of PML have been reported. The diagnosis of PML should be considered in any patient with new-onset or changes to pre-existing neurological manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may also occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI) and lumbar puncture (CSF testing for JC viral DNA). Therapy with Gazyvaro should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

The safety of immunisation with live or attenuated viral vaccines following Gazyvaro therapy has not been studied. Vaccination with live virus vaccines is not recommended during treatment and until B cell recovery.

Interactions

No drug-drug interaction studies have been performed. A risk of interactions with concomitantly used medicinal products cannot be excluded.

Pregnancy and lactation

Pregnancy

Gazyvaro should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of childbearing potential should use a reliable method of contraception during treatment with Gazyvaro and for 12 months thereafter (see Pharmacokinetics, Elimination). Newborns whose mothers have been exposed to Gazyvaro during pregnancy should not receive live vaccines until their B cell counts are within the normal range.

No studies have been conducted in pregnant women. A reproduction study in cynomolgus monkeys showed no evidence of teratogenic effects. However, treatment of pregnant cynomolgus monkeys with Gazyvaro resulted in complete depletion of B lymphocytes in the newborn. B cell counts in the newborn returned to normal levels and immunological function was restored within 6 months of birth (see Preclinical data, Teratogenicity).

Lactation

Because human IgG is excreted in human milk, and the potential for absorption and harm to the newborn is unknown, women should be advised to discontinue nursing during Gazyvaro therapy and for 12 months after the last dose of Gazyvaro. Animal studies have shown excretion of Gazyvaro in the milk (see Preclinical data, Teratogenicity).

Effects on ability to drive and use machines

No studies have been performed of the effects on the ability to drive and use machines. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

Undesirable effects

Clinical studies

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up in pivotal clinical trial BO21004/CLL11 in 336 patients treated with Gazyvaro.

The following frequency categories are used: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100).

Immune system disorders
Isolated cases: Anaphylaxis

Infections and infestations
Common: Urinary tract infection, oral herpes, rhinitis, (naso-)pharyngitis

Neoplasms, benign and malignant (including cysts and polyps)
Common: Squamous cell carcinoma of skin

Blood and lymphatic system disorders

Very common: Neutropenia (40.7%, grade 3-4: 34.9%), thrombocytopenia (15.4%, grade 3-4: 11.2%), anemia (12.4%, grade 3-4: 4.6%)
Common: Leukopenia

Metabolism and nutrition disorders

Common: Tumour lysis syndrome, hyperuricemia

Cardiac disorders
Common: Atrial fibrillation

Vascular disorders
Common: Hypertension

Respiratory disorders
Common: Cough

Gastrointestinal disorders

Very common: Diarrhea (10.4%, grade 3-4: 2.5%)

Common: Constipation
Uncommon: Transaminase elevation

Skin and subcutaneous tissue disorders
Common: Alopecia

Musculoskeletal disorders
Common: Arthralgia, back pain, chest pain

General disorders and administration-site reactions

Very common: Pyrexia (10.4%, grade 3-4: <1%), infusion reactions (68.9%, grade 3-4: 21.2%)
Common: Weight increased

Further information on selected adverse drug reactions
Infusion reactions

The incidence of infusion reactions was 65% with the infusion of the first 1000 mg of Gazyvaro (20% of patients experiencing a grade 3-4 infusion reaction, with no fatal events reported). Overall, 7% of patients experienced an infusion reaction leading to discontinuation of Gazyvaro. The incidence of infusion reactions with subsequent infusions was 3% with the second 1000 mg dose and 1% thereafter. No grade 3 5 infusion reactions were reported after the first 1000 mg infusion of cycle 1. In patients who received the combined measures for prevention of infusion reactions (adequate administration of a glucocorticoid and oral analgesic/antihistamine, interruption of antihypertensive medication in the morning of the first infusion and the cycle 1 day 1 infusion dose divided over 2 days), a trend towards decreased incidence of all-grade infusion reactions was observed. These measures did not appear to reduce the incidence of grade 3 4 infusion reactions. The symptoms most frequently reported in association with an infusion reaction were hypertension, headache, tachycardia and diarrhea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal edema and atrial fibrillation have also been reported (see Warnings and precautions).

Progressive multifocal leukoencephalopathy (PML)

PML has been reported in a patient treated with Gazyvaro for non-Hodgkin lymphoma (see Warnings and precautions).

Hepatitis B reactivation

Cases of hepatitis B reactivation have been reported in patients treated with Gazyvaro (see Warnings and precautions).

Overdosage

No experience with overdosage is available from human clinical trials. In clinical trials with Gazyvaro, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose-dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. It should be borne in mind that patients require regular monitoring of blood count and for increased risk of infections while B cell-depleted.

Properties and effects

ATC code: L01XC15

Mechanism of action and pharmacodynamics

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered type II anti-CD20 antibody of the IgG1 isotype. CD20 is expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes, but not on hematopoietic stem cells, pro B cells, normal plasma cells or other normal tissues. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, and macrophages and monocytes as compared to non-glycoengineered antibodies. In non-clinical studies, obinutuzumab induces direct cell death and mediates antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADCP) through recruitment of FcγRIII-positive effector cells. In addition, obinutuzumab mediates a low degree of complement-dependent cytotoxicity (CDC). In animal models, obinutuzumab mediates potent B cell depletion and antitumour efficacy.

Clinical efficacy

Chronic lymphocytic leukemia

A phase III, open-label, three-arm study (BO21004/CLL11) in two parts compared Gazyvaro plus chlorambucil with rituximab plus chlorambucil or chlorambucil alone in 781 patients with previously untreated chronic lymphocytic leukemia with comorbidities.

Patients had to have one or both of the following measures of coexisting medical conditions: comorbidity score (CIRS) of greater than 6 or reduced renal function (CrCl <70 ml/min). Patients with hepatic impairment and severe renal impairment were excluded from participating.

A total of 781 patients were randomised 2:2:1 to receive Gazyvaro plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1 compared Gazyvaro plus chlorambucil to chlorambucil alone in 356 patients and stage 2 compared Gazyvaro plus chlorambucil to rituximab plus chlorambucil in 663 patients. The median age was 73 years.

The most frequently reported coexisting medical conditions were: vascular disorders 73%, cardiac disorders 46%, gastrointestinal disorders 38%, metabolism and nutrition disorders 40%, renal and urinary disorders 38%, musculoskeletal and connective tissue disorders 33%.

The primary endpoint of the study was investigator-assessed progression-free survival. This was 26.7 months for Gazyvaro + chlorambucil vs 11.1 months for chlorambucil (HR 0.18 [95% CI 0.13, 0.24), p <0.0001) and 15.7 months for Mabthera + chlorambucil (HR 0.32 [95% CI 0.24, 0.44), p <0.0001). The difference Gazyvaro vs Mabthera was also significant with HR 0.39 (95% CI 0.31, 0.49), p<0.0001. Analysis by an independent review committee produced similar results. The response rate was 78.4% in the Gazyvaro + chlorambucil arm, 65% in the Mabthera + chlorambucil arm and 31.4% with chlorambucil alone. There have as yet been too few events for Kaplan-Meier analysis of overall survival.

26% of patients had molecular remission on treatment with Gazyvaro.

44% of patients treated with Gazyvaro plus chlorambucil were 75 years or older (median age was 73 years). These patients experienced more serious adverse events and adverse events leading to death than patients under 75 years of age. No significant differences in efficacy were observed between patients ≥75 years of age and those <75 years of age.

91% (40 out of 44) of evaluable patients treated with Gazyvaro displayed B cell depletion (defined as CD19+ B cell counts <0.07 × 109/l) at the end of the treatment period, which persisted during the 6-months of follow-up. Recovery of B cells was observed within 12 to 18 months of follow-up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease.

Immunogenicity

Patients in the pivotal trial, BO21004/CLL11, were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Gazyvaro. Seven out of 64 patients in the randomised phase and 2 out of 5 patients in the run-in phase tested positive for ATA at 12 months of follow-up. Of these patients, none experienced either anaphylactic or hypersensitivity reactions that were considered related to ATA, nor was clinical response impaired

Pharmacokinetics

Absorption

After the cycle 6 day 1 infusion, the C_{max} value in the population model was 510.6 μg/ml and the $AUC_{(T)}$ value was 10,113 μg*d/ml.

Distribution

The volume of distribution at steady state is 3.7.

Metabolism

The metabolism of Gazyvaro has not been directly studied. Antibodies are normally broken down in the liver like other proteins.

Elimination

The clearance of Gazyvaro after cycle 6 in CLL patients is approximately 0.085 l/day with an elimination half-life of approximately 34.4 days.

Pharmacokinetics in special patient groups

There are no significant differences in exposure between women and men. Thus no dose adjustment is required for gender.

Elderly patients

The population pharmacokinetic analysis of Gazyvaro showed no evidence that age affects the pharmacokinetics of Gazyvaro.

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of Gazyvaro in children.

Patients with renal impairment

No formal pharmacokinetic studies have been conducted in patients with renal impairment.

Patients with hepatic impairment

No formal pharmacokinetic studies have been conducted in patients with hepatic impairment.

Preclinical data

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Gazyvaro.

Mutagenicity

No studies have been performed to establish the mutagenic potential of Gazyvaro.

Impairment of fertility

No specific studies in animals have been performed to evaluate the effect of Gazyvaro on fertility. No adverse effects on male and female reproductive organs were observed in repeated-dose toxicity studies in cynomolgus monkeys.

Teratogenicity

An enhanced pre- and postnatal development (ePPND) toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received weekly intravenous Gazyvaro doses (mean $AUC_{0\ 168\ h}$ at steady state [on day 139 p.c.] was 125,000 and 250,000 [µg•h]/ml at 25 and 50 mg/kg, respectively; mean C_{max} was 1220 and 2470 µg/ml at 25 and 50 mg/kg, respectively) during gestation (organogenesis period; post-conception day 20 until delivery). Exposed offspring did not exhibit any teratogenic effects but B cells were completely depleted on day 28 postpartum. Offspring exposures on day 28 postpartum suggest that Gazyvaro can cross the blood-placenta-barrier. Serum concentrations in the newborn on day 28 postpartum were in the range of concentrations in maternal serum, whereas concentrations in milk on the same day were very low (less than 0.5% of the corresponding maternal serum levels), suggesting that exposure of the newborn must have occurred *in utero*. B cell counts returned to normal levels and immunological function was restored within 6 months of birth.

Other

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to recognition of the humanised antibody as foreign by cynomolgus monkeys (C_{max} and $AUC_{0\ 168\ h}$ at steady state [day 176] after weekly administration of 5, 25 and 50 mg/kg were 377, 1530 and 2920 µg/ml and 39,800, 183,000 and 344,000 [µg•h]/ml, respectively). Findings included acute anaphylactic or anaphylactoid reactions and an increased prevalence of systemic inflammation and infiltrates consistent with immune complex-mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulo-nephritis and serosal/adventitial inflammation. These reactions led to unscheduled euthanasia in 6/36 animals treated with Gazyvaro during dosing and recovery phases; these changes were partially reversible. Opportunistic infections were attributed to the pharmacological action of Gazyvaro.

Additional information

Incompatibilities

After dilution with 0.9% sodium chloride, no incompatibilities were observed between Gazyvaro in the concentration range 0.4 mg/ml to 20.0 mg/ml and polyvinyl chloride/poly-ethylene/polypropylene/polyolefin infusion bags or polyvinyl chloride (PVC)/polyurethane (PUR)/polyethylene (PE) infusion sets, nor with optional inline filters with product contact surfaces of polyethersulfone (PES), a 3-way polycarbonate (PC) stopcock or polyetherurethane (PEU) catheters. Do not shake or freeze the diluted product.

Diluents other than 0.9% NaCl solution should not be used to dilute Gazyvaro since their use has not been studied.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Stability of the prepared infusion solution

Gazyvaro does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Chemical and physical stability of the ready-to-use infusion solution has been demonstrated for 24 hours at 2 8°C, followed by 24 hours at ambient temperature (≤30°C), followed by an infusion taking no longer than 24 hours.

For microbiological considerations, the prepared infusion solution should be used immediately. If the prepared solution cannot be administered immediately, the storage time and conditions prior to administration are the responsibility of the user and should not normally exceed 24 hours at 2-8°C, unless dilution has taken place under controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2-8 °C). Store the container inside the outer package in order to protect the contents from light.

Do not freeze. Do not shake.

Keep out of the reach of children.

Instructions for handling and disposal

Gazyvaro should be prepared by a healthcare professional under aseptic conditions.

Withdraw 40 ml of Gazyvaro concentrate from the vial and dilute, for example, in PVC or PVC-free polyolefin infusion bags containing sterile, pyrogen-free 0.9% aqueous sodium chloride solution.

To preclude mix-ups between the two infusion bags for the initial 1000 mg dose, the recommendation is to utilise bags of different sizes to distinguish between the 100 mg dose for cycle 1 day 1 and the 900 mg dose for cycle 1 day 1 (continued) or day 2. To prepare the two infusion bags, withdraw 40 ml of Gazyvaro concentrate from the vial and dilute 4 ml in a 100 ml infusion bag and the remaining 36 ml in a 250 ml PVC or PVC-free polyolefin infusion bag containing sterile, pyrogen-free 0.9% aqueous sodium chloride solution. Clearly label all infusion bags.

Dose of Gazyvaro to be administered	Required amount of Gazyvaro concentrate
100 mg	4 ml
900 mg	36 ml
1000 mg	40 ml

Diluents other than 0.9% NaCl solution should not be used (see Incompatibilities).

Gently invert the infusion bag to mix the solution and avoid excessive foaming.

Parenteral drug products should be inspected visually for particulates and discolouration prior to administration

Disposal of unused and expired medicinal product

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Vials 1000 mg/40ml 1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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