Gazyva (obinutuzumab)

STRENGTH	DOSAGE FORM	ROUTE	GPID
1000mg/40mL	Vial	Intravenous	35532

MANUFACTURER

Genentech, Inc.

INDICATION(S)

Gazyva (obinutuzumab) is a CD20-directed cytolytic antibody and is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

DRUG CLASS

NEOPLASTIC DISEASE– ANTI-CD20 (B LYMPHOCYTE) MONOCLONAL ANTIBODY

PLACE IN THERAPY

Gazyva is a humanized monoclonal antibody that targets the CD20 antigen expressed on the surface of pre B-and mature B-lymphocytes and is approved for the treatment of patients with previously untreated CLL. It is a follow-on therapy to Rituxan (rituximab) which is a chimeric monoclonal antibody with the same mechanism of action. Although head-to-head data is not yet published, Gazyva appears to cause less immune reactions than Rituxan. Rituxan is indicated for the treatment of patients with previously untreated and previously treated CD20-positive CLL. Gazyva is also being evaluated in Phase III studies versus Rituxan for the treatment of indolent non-Hodgkin's lymphoma (GALLIUM study, results expected February 2017) and diffuse large B-cell lymphoma (GOYA study, results expected August 2015).

In 2013 there will be an estimated 15,680 new cases of CLL and 4,580 deaths from CLL. The cancer accounts for about one-third of the new cases of leukemia. The median survival is 8-10 years although the natural course of CLL can be variable with survival time ranging from 2-20 years or more depending on whether the disease is aggressive or indolent. The average person's lifetime risk of getting CLL is about 0.5 percent. The risk is slightly higher in men than in women. Factors such as having a family history of CLL may raise this risk. CLL mainly affects older adults. The average age at the time of diagnosis is around 72 years. It is rarely seen in people under age 40, and is extremely rare in children.

Cytogenetic abnormalities are present in about 80 percent of patients with previously untreated CLL; the most common abnormalities include:

- Del (13q) which is a deletion in chromosome 13q (55%)
- Del (11q) which is a deletion in chromosome 11q (18%)
- Trisomy 12 (16%)
- Del (17p) which is a deletion in chromosome 17p (7%)
- Del (6q) which is a deletion in chromosome 6q (7%)

Del (11q) is often associated with associated with extensive lymphadenopathy, disease progression, and shorter survival. Del (17p) is associated with worst outcomes, with short treatment free intervals, short median survival, and poor response to chemotherapy.

The National Comprehensive Cancer Network (NCCN) guidelines have not been updated since the approval of Gazyva. The recommended regimen varies based on initial treatment and refractory therapy along with the presence of genetic mutations including 11q and 17p deletions. The majority of regimens include Rituxan.

First-line therapy for CLL without del (11q) or del (17p), age ≥70 years or younger patients with comorbidities

- Leukeran ± Rituxan
- Treanda ± Rituxan
- Cyclophosphamide, prednisone ± Rituxan
- Rituxan
- Revlimid (lenalidomide)
- cladribine

First-line therapy for CLL without del (11q) or del (17p), age <70 years or older patients without significant comorbidities

- FCR (fludarabine, cyclophosphamide, Rituxan)
- FR (fludarabine, Rituxan)
- PCR (pentostatin, cyclophosphamide, Rituxan)
- Treanda ± Rituxan

Relapsed/refractory therapy for CLL without del (11q) or del (17p), age ≥70 years

- FCR
- PCR
- Treanda ± Rituxan
- High-dose methylprednisolone + Rituxan
- Leukeran ± Rituxan
- Arzerra
- Revlimid ± Rituxan
- Dose-dense Rituxan

Relapsed/refractory therapy for CLL without del (11q) or del (17p), age <70 years or older patients without significant comorbidities

- FCR
- PCR
- Treanda ± Rituxan
- RCHOP (Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone)
- R-HyperCVAD (Rituxan, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)
- Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, Rituxan)

- OFAR (oxaliplatin, fludarabine, cytarabine, Rituxan)
- Arzerra
- Revlimid ± Rituxan
- High-dose methylprednisolone + Rituxan

First-line therapy for CLL with del (17p)

- FCR
- FR
- High-dose methylprednisolone + Rituxan

Relapsed/refractory therapy for CLL with del (17p)

- RCHOP
- High-dose methylprednisolone + Rituxan
- R-HyperCVAD
- Arzerra
- Revlimid ± Rituxan
- OFAR

First-line therapy for CLL with del (11q)

- Treanda ± Rituxan
- FCR
- Leukeran ± Rituxan (only age ≥70 years with comorbidities)
- Cyclophosphamide, prednisone ± Rituxan (only age ≥70 years with comorbidities)
- Revlimid (only age ≥70 years with comorbidities)
- Rituxan (only age ≥70 years with comorbidities)
- PCR (only age <70 years or older patients without significant comorbidities)

Relapsed/refractory therapy for CLL with del (11q)

- FCR
- PCR
- Treanda ± Rituxan
- High-dose methylprednisolone + Rituxan
- Arzerra
- Revlimid ± Rituxan
- Leukeran ± Rituxan (only age ≥70 years with comorbidities)
- Dose-dense Rituxan (age ≥70 years with comorbidities)
- RCHOP (only age <70 years or older patients without significant comorbidities)
- R-HyperCVAD (only age <70 years or older patients without significant comorbidities)
- OFAR (only age <70 years or older patients without significant comorbidities)

EFFICACY

Gazyva was evaluated in a three arm, open-label, active control, randomized, multicenter trial (Study 1 in the prescribing information) in patients with previously untreated CD20+ chronic lymphocytic

leukemia requiring treatment and who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) <70 mL/min. Patients with CrCl <30 mL/min, active infections, positive hepatitis B (HBsAg or anti-HBc positive, patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, or immunization with live virus vaccine within 28 days prior to randomization were excluded from the trial. Patients were treated with chlorambucil control (Arm 1), Gazyva in combination with chlorambucil (Arm 2) or Rituxan in combination with chlorambucil (Arm 3). The safety and efficacy of Gazyva was evaluated in a comparison of Arm 1 vs. Arm 2 in 356 patients. Data comparing Arm 2 vs. Arm 3 is not currently listed in the prescribing information.

The majority of patients received 1000 mg of Gazyva on days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of Gazyva was divided between day 1 (100 mg) and day 2 (900 mg), which was implemented in 45 patients. Chlorambucil was given orally at 0.5 mg/kg on day 1 and day 15 of all treatment cycles (1 to 6).
In Study 1, the median age was 73 years, 60% were male, and 95% were Caucasian. Sixty-eight percent had a CrCl <70 mL/min and 76% had multiple coexisting medical conditions. Twenty-two percent of patients were Binet stage A, 42% were stage B and 36% were stage C. The median estimated CrCl was 61 mL/min. Eighty-one percent of patients treated with Gazyva in combination with chlorambucil received all 6 cycles compared to 67% of patients in the chlorambucil alone arm. Cytogenetic abnormalities were not reported.

The median progression free survival (PFS) in the Gazyva in combination with chlorambucil arm was 23.0 months and 11.1 months in the chlorambucil alone arm (median observation time 14.2 months) as assessed by independent review and is consistent with investigator assessed PFS.

Efficacy Results for Study 1 *(From Gazyva Prescribing Information)*

Endpoint	GAZYVA + Chlorambucil	Chlorambucil
Median Progression-Free Survival [a]	23.0 months (HR 0.16 [0.11; 0.24], p-value <0.0001 stratified log-rank test)	11.1 months
Overall Response Rate [b]	75.9%	32.1%
Complete Response	27.8%	0.9%
Median Duration of Response	15.2 months	3.5 months

[a] As defined by independent review. Investigator assessed PFS was consistent with data from independent review.
[b] As defined as best overall response rate (ORR=CR+PR)

Updated data from study 1 is now available in the form of a company press release. They report median PFS of 26.7 months for patients in the Gazyva arm compared with 15.2 months for those in the Rituxan arm (HR 0.39, p<0.0001). No new safety signals were observed for either Gazyva or Rituxan. Additional data comparing the Gazyva and Rituxan treatment arms showed higher complete response rates (21 percent compared with 7 percent) and a ten-fold increase in the percentage of people achieving minimal residual disease (MRD) negativity (29.4 percent compared with 2.5 percent), which was defined as no detectable disease in the blood at the end of the treatment course.

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SAFETY

Gazyva has a boxed warning for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy. Warnings and precautions include: infusion reactions, tumor lysis syndrome, neutropenia, thrombocytopenia, and immunization. The most common adverse reactions (incidence ≥10%) were: infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorder.

Gazyva is pregnancy category C. No formal drug interaction studies have been conducted with Gazyva.

DOSAGE

Gazyva is administered intravenously for 6 treatment cycles of 28 days each. The initial cycle of Gazyva dosing is 100mg on day 1, 900mg on day 2, then 1000mg on days 8 and 15. On cycles 2-6 Gazyva is administered as 1000mg on day 1.

Patients should be premedicated with glucocorticoids, acetaminophen, and an antihistamine before infusion. Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

Gazyva is administered only as an intravenous infusion through a dedicated line; do not administer as an intravenous push or bolus. Monitor blood counts at regular intervals. Gazyva should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

COST

Drug	Cost/unit	Cost per 28 Days
Gazyva (obinutuzumab) 1000mg vial; IV 100mg on day 1 Cycle 1, 900mg on day 2 Cycle 1, 1000mg on day 8 and 15 of Cycle 1, 1000mg on day 1 of Cycles 2-6	AWP=$6192	Cycle 1: $18,576 Cycles 2-6: $6192
Rituxan (rituximab) 100mg vial, 500mg vial; 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2−6, in combination with fludarabine and cyclophosphamide, administered every 28 days	AWP=$801; $4006	Cycle 1: $6409^ Cycles 2-6: $8012^
Leukeran (chlorambucil) 2mg tablet; PO 0.5 mg/kg on day 1 and day 15 of all treatment cycles	AWP=$11.14	$557*
Cyclophosphamide 25mg, 50mg tablet; 500mg, 1000mg vial; 250 mg/m^2/day IV on days 1-3 every 28 days for up to 6 cycles; 150 mg/m^2/day PO on days 1-5 every month for up to 6 cycles	MAC=$1.59; $2.68 AWP=$339; $679	$80 (PO)^ $1017 (IV)^
Fludarabine 50mg/2mL vial 25 mg/m^2 IV once daily for 5 days every 28 days	AWP=$240	$1200^
Treanda (bendamustine) 25mg, 100mg vial; 100mg/m^2 IV on days 1 and 2 repeated every 28 days for up to 6 cycles	AWP=$615; $2460	$9840^
Arzerra (ofatumumab) 100mg, 1000mg vial; 300mg IV once followed 1 week later by 2000mg IV weekly for 7 additional	AWP=$551; $5507	Initial 56 days: $78,744 Maintenance: $11,013

weeks; then give 2000mg IV once monthly for 4 infusions (total of 12 doses over 24 weeks)		
Revlimid (lenalidomide) 2.5, 5, 10, 15, 20, 25mg capsule; 5mg PO daily for 56 days, then titrated up to 25mg daily	AWP=$495; $495; $503; $505; $510; $510	Initial: $13,860# Maintenance: $14,280#

^Assuming a patient with a BSA of $2m^2$
*Assuming patient weighing 100kg
#Not FDA approved for CLL

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider ADDING Gazyva to the formulary pending complete review by the appropriate oversight committee for the plan.

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