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MEDICAL POLICY – 5.01.582

Antibody-Drug Conjugates

Effective Date:	Aug. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	July 22, 2024	None
Replaces:	N/A	

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Introduction

An antibody is a blood protein. When the immune system detects an unhealthy cell, antibodies link to a molecule, known as an antigen, on the unhealthy cell. Monoclonal antibodies are produced in a laboratory. They are made to link to antigens usually found in high numbers on cancer cells. Antibody-drug conjugates combine monoclonal antibodies with certain chemotherapy drugs. The monoclonal antibodies find the cancer cells and the chemotherapy drug is released directly into those cells. The goal with this treatment is to target only cancer cells and spare nearby healthy cells. This policy describes when specific antibody-drug conjugates may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Besponsa (inotuzumab ozogamicin) IV	**Besponsa (inotuzumab ozogamicin) may be considered medically necessary when all the following are met:** • The individual is 1 year of age or older **AND** • The individual has been diagnosed with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL)
Elahere (mirvetuximab soravtansine-gynx)	**Elahere (mirvetuximab soravtansine-gynx) may be considered medically necessary when all the following are met:** • The individual is 18 years of age or older **AND** • The individual has been diagnosed with folate receptor alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer **AND** • The individual has received one or more prior systemic treatment regimens
Mylotarg (gemtuzumab ozogamicin) IV	**Mylotarg (gemtuzumab ozogamicin) may be considered medically necessary for the treatment of individuals with:** • Newly-diagnosed CD33+ Acute Myeloid Leukemia (AML) in adults and pediatric individuals 1 month and older **OR** • Diagnosis of relapsed or refractory CD33+ AML in adults and in pediatric individuals 2 years and older

Padcev (enfortumab vedotin-ejfv) IV	**Padcev (enfortumab vedotin-ejfv) may be considered medically necessary for the treatment of locally advanced or metastatic urothelial cancer (mUC) for adult individuals when the following criteria are met:**
	• As a single agent:
	  ○ Individuals who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy
	  OR
	  ○ Individuals who have previously received a programmed death receptor-1 (PD-1) (eg, Keytruda) or programmed death-ligand 1 (PD-L1) inhibitor (eg, Imfinzi, Tecentriq,

Drug	Medical Necessity
	Bavencio) and a platinum-containing chemotherapy (eg, cisplatin, carboplatin, oxaliplatin) • In combination with pembrolizumab
Tivdak (tisotumab vedotin-tftv) IV	**Tivdak (tisotumab vedotin-tftv) may be considered medically necessary for the treatment of adult individuals with:** • Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
Zynlonta (loncastuximab tesirine-lpyl) IV	**Zynlonta (loncastuximab tesirine-lpyl) may be considered medically necessary for the treatment of adult individuals with:** • Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) may be approved up to 3 months.** **Elahere (mirvetuximab soravtansine-gynx), Padcev (enfortumab vedotin-ejfv), Tivdak (tisotumab vedotin-tftv), and Zynlonta (loncastuximab tesirine-lpyl) may be approved up to 6 months.**
Re-authorization criteria	**Future re-authorization for Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) may be approved up to 6 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

	Future re-authorization of Elahere (mirvetuximab soravtansine-gynx), Padcev (enfortumab vedotin-ejfv), Tivdak (tisotumab vedotin-tftv), and Zynlonta (loncastuximab tesirine-lpyl) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J3590	Unclassified biologics
J9063	Injection, mirvetuximab soravtansine-gynx (Elahere), 1 mg
J9177	Injection, enfortumab vedotin-ejfv (Padcev), 0.25 mg
J9203	Injection, gemtuzumab ozogamicin (Mylotarg), 0.1 mg
J9229	Injection, inotuzumab ozogamicin (Besponsa), 0.1 mg
J9273	Injection, tisotumab vedotin-tftv, (Tivdak) 1 mg
J9359	Injection, loncastuximab tesirine-lpyl, (Zynlonta) 0.075 mg

Related Information

Consideration of Age

The ages stated in this policy for which Besponsa (inotuzumab ozogamicin), Elahere (mirvetuximab soravtansine-gynx), Mylotarg (gemtuzumab ozogamicin), Padcev (enfortumab vedotin-ejfv), Tivdak (tisotumab vedotin-tftv), and Zynlonta (loncastuximab tesirine-lpyl) are considered medically necessary are based on the FDA labeling for these drugs.

Benefit Application

The drugs in this policy are managed through the medical benefit.

Evidence Review

Background

Mechanism of Action

Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) are antibody drug conjugates (ADCs) that are composed of 3 important components: the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody (being either inotuzumab or gemtuzumab), N-acetyl gamma-calicheamicin (or for short calicheamicin), and an acid-cleavable linker. Calicheamicin covalently binds to the monoclonal antibody through the linker. The complex mechanism begins when the ADC binds to receptors on CD22 (if inotuzumab) or CD33 (if gemtuzumab) expressing tumor cells and internalize forming an endosome. This complex fuses with lysosomes, leading to degradation of the acid labile linker and intracellular release of calicheamicin. Calicheamicin activation breaks double-stranded DNA, causing downstream effects such as cell cycle arrest and eventual cell apoptosis.

Elahere (mirvetuximab soravtansine-gynx) is an ADC. The antibody is a chimeric IgG1 directed against folate receptor alpha (FRα). The small molecule, DM4, is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FRα, mirvetuximab soravtansine-gynx is internalized followed by intracellular release of DM4 via proteolytic cleavage. DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.

Padcev (enfortumab vedotin-ejfv) is an ADC. The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin-ejfv is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death.

Tivdak (tisotumab vedotin-tftv) is a tissue factor (TF)-directed ADC. The antibody is a human IgG1 directed against cell surface TF. TF is the primary initiator of the extrinsic blood coagulation cascade. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggests that the anticancer activity of tisotumab vedotin-tftv is due to the binding of the ADC to TF expressing cancer cells, followed by internalization of the ADC-TF complex, and release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. In vitro, tisotumab vedotin-tftv also mediates antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

Zynlonta (loncastuximab tesirine-lpyl) is a CD19-directed antibody and alkylating agent conjugate, consisting of a humanized IgG1 kappa monoclonal antibody conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent, through a protease-cleavable valine-alanine linker. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. Upon binding to CD19, loncastuximab tesirine-lpyl is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.

Summary of Evidence

Besponsa (inotuzumab ozogamicin)

INO-VATE ALL

INO-VATE ALL was an open-label, two-group, randomized (1:1), phase III trial which assessed efficacy and safety of inotuzumab ozogamicin compared to standard intensive chemotherapy in adult individuals with r/r ALL. Individuals were randomized based on duration of first remission (<12 months or ≥ 12 months), salvage therapy (Salvage 1 or 2) and individual age (<55 or ≥ 55

years). The target population were adult individuals who were 18 years or age and older with r/r ALL that had ≥70% leukemic blast cells exhibiting CD22, determined by flow cytometry. Individuals were randomized to receive either inotuzumab 1.8mg/m^2 per cycle (in a fractionated schedule of 0.8mg/m^2 on Day 1 of each cycle and 0.5mg/m^2 on Days 8 and 15), or the investigators' choice of one of three standard of care regimens: fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG), cytarabine plus mitoxantrone (CM) or high dose cytarabine (HIDAC). Efficacy of the study was determined by two primary endpoints: CR/CRi and overall survival. In addition to CR/CRi results, important secondary endpoints that helped evaluate efficacy were MRD and duration of remission. CR/CRi was pre-specified to include the first 218 individuals (109 in the inotuzumab ozogamicin group and 109 in standard chemotherapy) that underwent randomization in the intention-to-treat analysis.

From the 218 individuals, 88 individuals receiving inotuzumab ozogamicin responded to therapy. About 64/88 (73%) and 21/88 (24%) achieved CR/CRi in Cycle 1 and Cycle 2 respectively of therapy. In the investigator's choice of chemotherapy arm, only 32 individuals responded with 29/32 (91%) of Cycle 1 and 1/32 (3%) of Cycle 2, achieving CR/CRi. The overall rate of CR/CRi in the inotuzumab group was significantly higher (80.7%, CI: 72.1-87.7%) vs. standard chemotherapy (29.4%, CI: 21-38.8%; $p < 0.001$). The number of individuals who had MRD-negativity in the inotuzumab group were 69/88 (78.4%; 95% CI: 68.4-86.5) compared to the standard chemotherapy group where only 9/32 (28.1%) had MRD-negative disease. The median duration of remission was 5.4 months in the inotuzumab ozogamicin group (95% CI: 4.2-8.0), and 3.5 months in the standard chemotherapy group (95% CI: 2.9-6.6).

In the survival analysis, the ITT population's median overall survival was 7.7 months (95%CI: 6.0 to 9.2) vs. 6.2 months (95%CI: 4.7-8.3) and the hazard ratio was 0.75 (97.5% CI: 0.57 to 0.99). The analysis of the OS did not meet pre-specified boundary of statistical significance. In addition, the proportion of individuals who went on to HSCT were 79/164 (48%) in the inotuzumab ozogamicin group vs. 35/162 (22%) in the investigator's choice of chemotherapy.

Elahere (mirvetuximab soravtansine-gynx)

The efficacy of Elahere was evaluated in Study 0417 (NCT04296890), a single-arm trial of individuals with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (n=106). Individuals were permitted to receive up to three prior lines of systemic therapy. All individuals were required to have received prior bevacizumab. The trial enrolled individuals whose tumors were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Individuals were excluded if they had corneal

disorders, ocular conditions requiring ongoing treatment, Grade >1 peripheral neuropathy, or noninfectious interstitial lung disease.

Individuals received Elahere 6 mg/kg (based on adjusted ideal body weight) as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed overall response rate (ORR) and duration of response (DOR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The efficacy evaluable population included 104 individuals with platinum-resistant disease, who had measurable disease, and received at least one dose of Elahere. In these 104 individuals, the median age was 62 years (range: 35 to 85); 96% were White, 2% were Asian, and 2% did not have race reported. Two percent of individuals were Hispanic or Latino. All individuals had an ECOG PS of 0 (57%) or 1 (43%). Ten percent of individuals had received 1 prior line of systemic therapy, 39% of individuals had received 2 prior lines of systemic therapy, and 50% of individuals had received 3 prior lines of systemic therapy. All individuals had received prior bevacizumab and 47% had received a prior PARP inhibitor. The confirmed ORR was 31.7% (95% CI: 22.9%; 41.6%) with 4.8% of individuals achieving a complete response and 26.9% achieving a partial response rate. The median DOR was 6.9 months (95% CI: 5.6 months; 9.7 months).

Mylotarg (gemtuzumab ozogamicin)

SWOG S0106

The FDA granted accelerated approval of gemtuzumab ozogamicin in May 2000 based on three phase II pilot studies in 142 adult individuals with AML. This study aimed to examine the CR rate with the addition of gemtuzumab ozogamicin with standard induction chemotherapy compared to standard chemotherapy alone. Disease-free survival post-consolidation of the two comparator groups was also evaluated. Individuals were randomized (stratified by age <35 vs ≥35) to receive induction therapy with daunorubicin (45 mg/m^2 days 1-3), cytarabine (100mg/m^2 on days 1-7) and gemtuzumab ozogamicin (6 mg/m^2 on day 4) versus standard induction therapy with daunorubicin (60 mg/m2 days 1-3) and cytarabine (100mg/m2/ days 1-7). The results showed that 150/277 (66%) individuals treated in the gemtuzumab ozogamicin cohort had a CR. This compared to 159/229 (69%) of individuals who achieved CR with just chemotherapy alone (p <0.0025). Disease-free survival was not improved and fatal toxicity for individuals in the gemtuzumab ozogamicin cohort vs. standard chemotherapy was 16/283 (16%) vs. 4/281 (1.4%), respectively. Pfizer voluntarily removed the drug from commercial marketing in 2010.

Gemtuzumab ozogamicin is now back in the commercial market based on three studies mentioned by the FDA:

- ALFA-0701 This was a randomized, open-label phase III trial with 271 individuals who were newly-diagnosed with de novo AML from ages 50-70 years old. Individuals were randomized (1:1) in receiving standard chemotherapy with gemtuzumab ozogamicin, and those with just standard chemotherapy. Efficacy was established on EFS (event-free survival), measured from date of randomization until induction failure, relapse, or death by any cause. Individuals received induction therapy consisting of daunoruicin 60mg/m^2 on Days 1-3), cytarabine (200mg/m^2 on Days 1-7) and with (or without as a comparator) gemtuzumab ozogamicin at 3mg/m^2 on Days 1, 4, and 7. Results showed that estimated median EFS was 17.3 months for individuals receiving the therapy combination in comparison to 9.5 months with just standard chemotherapy. The hazard ratio was 0.66 (95% CI: 0.42-0.76).
- AML-19 This study was a randomized open-label phase III trial with 237 participants that looked at gemtuzumab ozogamicin monotherapy vs. best supportive care. Individual criteria included individuals that were ≥ 75 or 61-75 years with a World Health Organization performance status (WHO-PS) greater than 2 or were unwilling to receive intensive chemotherapy. Individuals in the gemtuzumab ozogamicin arm got induction therapy of 6mg/m^2, then 3mg/m^2 on at 2mg/m^2 on Day 1 every 4 weeks for a total of 8 courses. Efficacy was established on improvement in overall survival (OS). Hazard ratio for OS was 0.69 (95%CI: 0.53-0.90). The median OS was 4.9 months (gemtuzumab ozogamicin cohort) vs. 3.6 months (best supportive care).
- MyloFrance-1 This study was a phase II, single-arm, open-label study with 57 individuals with CD33-positive r/r AML. Individuals received a single dose of gemtuzumab ozogamicin 3mg/m^2 on days 1, 4, and 7 of therapy. Consolidation therapy consisted of cytarabine q12h for 3 days. Efficacy was established on CR and duration of remission. About 15/57 (26%) achieved CR and median relapse-free survival was 11.6 months. This was measured from first documentation of CR to the date of relapse/death.

Padcev (enfortumab vedotin-ejfv)

The efficacy of enfortumab vedotin-ejfv in urothelial carcinoma was evaluated in 2 pivotal trials, EV-201 and EV-301, at time of review, only data from Cohort 1 of EV-201 was available. EV-201 was a Phase II study evaluating the efficacy and safety of enfortumab vedotin-ejfv at a dose of 1.25 mg/kg IV administered during days 1, 8 and15 every 28-day cycle in adults with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum

chemotherapy and anti-PD-1 or PD-L1. The primary efficacy outcome was confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR) when enrollment is completed in Cohort 1, and all individuals in the cohort have been followed for at least 6 months, or have discontinued from study, or had 30 days safety follow-up after PD, whichever comes first. Secondary outcomes included but were not limited to duration of response and progression-free survival assessed by BICR and investigator, objective response rate assessed by investigator and overall survival, safety, and tolerability.

Per protocol objective response rate was 44%, with a median time to response of 1.84 months (1.2 to 9.2) and median duration of response was 7.6 months. At time of analysis of this publication, 44% of all responders had ongoing responses to treatment with a 12% complete response ranging from 3.61 to 11.31 months. The primary endpoint for EV-201 is comparable to Phase II data from erdafitinib, an oral kinase inhibitor that is considered subsequent therapy for individuals with FGFR3 or FGFR2 genetic alterations. A complete response duration of 3.61 months to 11.31 months is clinically meaningful, given the need for additional therapies for individuals with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy.

The efficacy of enfortumab vedotin in combination with pembrolizumab was evaluated in individuals with locally advanced or metastatic urothelial carcinoma in multi-cohort study, EV-103/Keynote-869. Dose escalation cohort and cohort A, single-arm cohorts, included individuals who received pembrolizumab in combination with enfortumab vedotin, while cohort K included individuals who were randomized to receive either pembrolizumab in combination with enfortumab vedotin or enfortumab alone. In these studies, patients did not receive prior systemic therapy and were not eligible for cisplatin-containing chemotherapy. A total 121 individuals received the combination therapy where the individuals' objective response rate (ORR) and duration of response (doR) were evaluated. The individuals' overall response rate was 68% including 12% of individuals with complete response. The median doR for the dose escalation cohort plus cohort A was 22 months, and the medial doR was not reached for cohort K.

Tivdak (tisotumab vedotin-tftv)

The efficacy of tisotumab vedotin-tftv was evaluated in innovaTV 204 (NCT03438396), an open-label, multicenter, single-arm trial that treated 101 individuals with recurrent or metastatic cervical cancer who had received no more than two prior systemic regimens in the recurrent or metastatic setting, including at least one prior platinum-based chemotherapy regimen.

Individuals were excluded if they had active ocular surface disease, any prior episode of cicatricial conjunctivitis or Stevens Johnson syndrome, Grade ≥2 peripheral neuropathy or known coagulation defects leading to an increased risk of bleeding. Individuals received tisotumab vedotin-tftv 2 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments were performed every 6 weeks for the first 30 weeks and every 12 weeks thereafter.

The median age was 50 years (range: 31 to 78); 95% were White, 2% were Asian, and 1% were Black. Six percent of individuals were Hispanic or Latino. Sixty-eight percent of individuals had squamous cell carcinoma, 27% had adenocarcinoma, and 5% had adenosquamous histology. ECOG performance status was 0 (58%) or 1 (42%). Seventy percent of individuals had received 1 prior line of systemic therapy, and 30% had 2 prior lines of systemic therapy. Sixty-nine percent of individuals previously received bevacizumab as part of their prior systemic therapy. Sixty-three percent received bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or carboplatin, or paclitaxel and topotecan) as first-line therapy. The major efficacy outcome measures were confirmed objective response rate (ORR) as assessed by an independent review committee (IRC) using RECIST v1.1 criteria and duration of response (DOR). The confirmed ORR was 24% (95% CI: 15.9%; 33.3%) with 7% of individuals achieving a complete response and 17% achieving a partial response rate. The median DOR was 8.3 months (95% CI: 4.2 months; not reached).

Zynlonta (loncastuximab tesirine-lpyl)

LOTIS-2

LOTIS-2 was an open-label, single-arm trial in 145 adult individuals with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior systemic regimens. The trial excluded individuals with bulky disease and active central nervous system lymphoma. Individuals received Zynlonta 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity.

Of the 145 individuals enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an ECOG performance status of 0 to 1. Race was reported in 97% of individuals; of these individuals, 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy.

Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. The median follow-up time was 7.3 months (range 0.3 to 20.2). The confirmed ORR by IRC with Zynlonta was 48.3% (95% CI: 39.9%-56.7%) and the duration of overall response was a median of 10.3 months (95% CI: 6.9 – NE [not estimable]). The median time to response was 1.3 months (range 1.1 to 8.1).

Safety/Tolerability

Besponsa (inotuzumab ozogamicin)

INO-VATE ALL trial observed 23/164 individuals (14%) who had hepatotoxicity and hepatic veno-occulsive disease (VOD). VOD was reported up to 56 days from the last dose of treatment of inotuzumab ozogamicin, without intervening HSCT. In the study, 79 individuals were able to proceed to subsequent HCT and 18/79 individuals had VOD. There were 5/18 individuals in the inotuzumab arm that had a fatal episode of VOD. The signs of VOD were observed at a mean of 15 days (range: 3-57days).

Thrombocytopenia and neutropenia were one of the most common AEs seen in the INO-VATE ALL trial that included 83/164 individuals (51%) and 81/164 individuals (49%) respectively. Grade 3 or 4 thrombocytopenia events occurred in 23/164 (14%) individuals. In regard to neutropenia, 33/164 individuals (20%) and 45/164 individuals (27%) had Grade 3 or Grade 4 neutropenia respectively. Febrile neutropenia occurred in 43/164 individuals (26%). Hemorrhagic events accounted for 54/164 individuals (33%), with 5% who had either a Grade 3 or 4. One individual died from an intra-abdominal hemorrhage. Most observed hemorrhagic events were epistaxis in 24/164 individuals (15%).

Individuals who were in the inotuzumab arm had a higher day 100 post-HSCT mortality rate. There were 79/164 individuals in the inotuzumab cohort and 35/162 individuals in the investigator's choice of therapy who were able to do a follow-up transplant. Individuals who underwent HSCT showed that 31/79 individuals (39%) in the inotuzumab cohort vs. 8/35 (23%) in the investigator's choice of therapy had passed away within 100 days post-HSCT. The most common causes of death include VOD, multi-organ failure (MOF), infection or a mix of them together.

Elahere (mirvetuximab soravtansine-gynx)

The safety of Elahere was evaluated in Study 0417, a single-arm, open-label study in individuals (n=106) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Serious adverse reactions occurred in 31% of individuals. The most common (≥2%) serious adverse reactions were intestinal obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). Fatal adverse reactions occurred in 2% of individuals, including small intestinal obstruction (1%) and pneumonitis (1%).

Permanent discontinuation of Elahere due to adverse reactions occurred in 11% of individuals. The most common (≥2%) adverse reactions leading to permanent discontinuation were intestinal obstruction (2%) and thrombocytopenia (2%). One individual (0.9%) permanently discontinued Elahere due to visual impairment (unilateral decrease to BCVA < 20/200 that resolved to baseline after discontinuation).

Dosage delays of Elahere due to an adverse reaction occurred in 39% of individuals treated with Elahere. Adverse reactions which required dosage delays in ≥3% of individuals included visual impairment (15%), keratopathy (11%), neutropenia (6%), dry eye (5%), cataracts (3%), and increased gamma-glutamyltransferase (3%).

Dose reductions of Elahere due to an adverse reaction occurred in 20% of individuals. Adverse reactions which required dose reductions in ≥3% of individuals included visual impairment (9%) and keratopathy (7%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, were vision impairment, fatigue, increased aspartate aminotransferase, nausea, increased alanine aminotransferase, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neutrophils, and decreased hemoglobin.

Mylotarg (gemtuzumab ozogamicin)

Combination Therapy in Newly-Diagnosed Do Novo CD33+ AML

Safety data from ALFA-0701 showed discontinuation due to any AEs occurred in 21% of individuals in the gemtuzumab ozogamicin combination therapy vs. 7% in the DA group (dauarubicin and cytarabine). The most frequent causes of discontinuations were due to thrombocytopenia (15%), VOD (3%), and septic shock (2%). Fatal adverse reactions occurred in 8 individuals (6%) in the gemtuzumab ozogamicin arm compared to 3 individuals (2%) in the DA arm. Causes of death include 3 that died from VOD, 4 from hemorrhage-related events, and 1

individual due to suspected cardiac cause. A large proportion of individuals that had ≥ Grade 3 AEs were due to infection and hemorrhage during both induction and consolidation phases of therapy.

Monotherapy for Newly Diagnosed CD33+ AML

Safety data from AML-19 showed death due to any AE in 19 individuals in the gemtuzumab ozogamicin arm compared to 23 individuals in the best supportive care arm. There were 39 out of 111 individuals with Grade ≥ 3 infection and 20 out of 111 individuals with Grade ≥ 3 febrile neutropenia in the gemtuzumab ozogamicin arm, but those were comparable with best supportive care.

Padcev (enfortumab vedotin-ejfv)

The most common adverse reactions with Padcev in EV-301 included rash (54%), fatigue (50%), peripheral neuropathy (50%), alopecia (47%), decreased appetite (41%), diarrhea (35%), nausea (30%), pruritus (34%), dysgeusia (26%), anemia (20%), weight decreased (16%), pyrexia (22%), musculoskeletal pain (25%), dry eye (24%), urinary tract infection (17%), hemorrhage (17%), and dry skin (17%). There is a black box warning that Padcev can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Tivdak (tisotumab vedotin-tftv)

The most common adverse reactions with Tivdak in TV-204 included hemoglobin decreased (52%), fatigue (50%), lymphocytes decreased (42%), nausea (41%), peripheral neuropathy (39%), alopecia (39%), epistaxis (39%), conjunctival adverse reactions (37%), hemorrhage (32%), leukocytes decreased (30%), creatinine increased (29%), dry eye (29%), prothrombin international normalized ratio increased (26%), activated partial thromboplastin time prolonged (26%), diarrhea (25%), and rash (25%). There is a black box warning that Tivdak caused changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration.

Zynlonta (loncastuximab tesirine-lpyl)

The most common adverse reactions with Zynlonta are thrombocytopenia (58%), increased gamma-glutamyltransferase (57%), neutropenia (52%), anemia (51%), hyperglycemia (48%), transaminase elevation (41%), fatigue (38%), hypoalbuminemia (37%), rash (30%), edema (28%), nausea (23%), and musculoskeletal pain (23%). There are warnings and precautions regarding effusion and edema, myelosuppression, infections, cutaneous reactions, and embryo-fetal toxicity.

Practice Guidelines and Position Statements

Table 1. NCCN Guidelines: Recommended Regimens for r/r B-cell Acute Lymphoblastic Leukemia (ALL)

R/R Ph-Positive B-ALL	R/R Ph-Negative B-ALL
TKI (dasatinib, imatinib, ponatinib, nilotinib, or bosutinib) Blinatumomab ± TKI Inotuzumab ozogamicin ± TKI Tisagenlecleucel (individuals < 26 years of age with refractory disease or ≥ 2 relapses and failure of 2 TKIs) Brexucabtagene autoleucel (following therapy that has included TKIs)	Inotuzumab ozogamicin (for B-ALL only) Blinatumomab (for B-ALL only) Tisagenlecleucel (for B-ALL only) (individuals < 26 years of age with refractory disease or ≥ 2 relapses) Brexucabtagene autoleucel (for B-ALL only)

Table 2. NCCN Guidelines: Therapy for r/r Acute Myeloid Leukemia (AML)

Targeted Therapy	Aggressive Therapy for Appropriate Patients	Less Aggressive Therapy
FLT3-ITD mutation ○ Gilteritinib ○ Hypomethylating agents (azacitidine or decitabine) + sorafenib FLT3-TKD mutation ○ Gilteritinib	Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin HiDAC (if not received previously in treatment) ± idarubicin or daunorubicin or mitoxantrone)	Hypomethylating agents (azacitidine or decitabine) LDAC (category 2B) Venetoclax + HMA/LDAC

IDH2 mutation ○ Enasidenib IDH1 mutation ○ Ivosidenib CD-33 positive ○ Gemtuzumab ozogamicin	Fludarabine + cytarabine + G-CSF ± idarubicin Etoposide + cytarabine ± mitoxantrone Clofarabine ± cytarabine ± idarubicin	

2019 Update

A literature search from 1/1/18 to 2/28/19 found no new evidence that would require a change in this policy.

2020 Update

Reviewed prescribing information for all drugs in policy. Added an expanded indication that includes pediatric coverage identified for Mylotarg (gemtuzumab ozogamicin) for newly diagnosed CD33+ AML in adults and pediatric individuals 1 month and older. Added a separate Investigational table and a Documentation Requirements table.

2021 Update

Added a new antibody-drug conjugate to policy called Zynlonta (loncastuximab tesirine-lpyl) which is a CD19-directed antibody and alkylating agent conjugate approved for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Reviewed prescribing information for Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) and no new information was identified that would require a change in this policy for these two medications.

2022 Update

Added a new antibody-drug conjugate to policy called Elahere (mirvetuximab soravtansine-gynx) which is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult individuals with FRα positive, platinum-resistant

epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Reviewed prescribing information for all other ADC's in policy. No new information was identified that would require a change in this policy for Besponsa, Mylotarg, Padcev, Tivdak, or Zylonta.

2023 Update

Reviewed prescribing information of all drugs in this policy. Updated Padcev coverage criteria to include recently approved indication of using Padcev in combination with pembrolizumab for the treatment of adult individuals with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy.

2024 Update

Reviewed prescribing information of all drugs in this policy. Updated Padcev (enfortumab vedotin-ejfv) to include coverage criteria for the treatment of locally advanced or metastatic urothelial cancer in combination with pembrolizumab regardless of cisplatin-containing chemotherapy eligibility. Updated Besponsa (inotuzumab ozogamicin) age requirement from 18 to 1 year of age or older.

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History

Date	Comments
02/01/18	New policy, approved January 16, 2018. Add to Prescription Drug section. Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) may be considered medically necessary when criteria are met; considered investigational when criteria are not met.
01/01/19	Coding update, added new HCPCS code J9229 (new code effective 1/1/19).
04/01/19	Annual Review, approved March 19, 2019. Updated literature search; no changes. Removed HCPC codes J3490 and J3590.
08/01/20	Annual review, approved July 23, 2020. Updated coverage criteria for Mylotarg (gemtuzumab ozogamicin) and added an expanded indication that includes pediatric coverage for newly diagnosed CD33+ AML in patients 1 month and older.
06/01/21	Annual Review, approved May 11, 2021. Added criteria for Zynlonta (loncastuximab tesirine-lpyl) for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Added HCPCS code J3590.
10/01/21	Coding update, Added HCPCS code C9084.
01/01/22	Interim Review, approved December 14, 2021. Added criteria for Tivdak (tisotumab vedotin-tftv) for the treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Moved Padcev (enfortumab vedotin-ejfv) to Policy 5.01.582 from Policy 5.01.540 with no changes to coverage criteria. Added HCPCS code J9177.
04/01/22	Coding update. Added term date to HCPC code C9084. Added new HCPC codes J9273 and J9359.
01/01/23	Annual Review, approved December 13, 2022. Added coverage for Elahere (mirvetuximab soravtansine-gynx) for the treatment of adults with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one or more prior systemic treatment regimens. Changed the wording from "patient" to "individual" throughout the policy for standardization. Added new drug name Elahere to HCPC code J3590.
04/01/23	Coding update. Added new HCPCS code C9146 Removed deleted HCPCS code C9084. Removed Tivdakand Zynlonta from HCPC code J3590.
06/01/23	Annual Review, approved May 9, 2023. Updated Padcev coverage criteria to include use in combination with pembrolizumab for the treatment of adult individuals with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy.
07/01/23	Coding update. Added new HCPC code J9063 and removed termed HCPC code C9146.

Date	Comments
04/01/24	Annual Review, approved March 12, 2024. Updated Padcev (enfortumab vedotin-ejfv) to include coverage criteria for the treatment of locally advanced or metastatic urothelial cancer in combination with pembrolizumab regardless of cisplatin-containing chemotherapy eligibility.
08/01/24	Interim Review, approved July 22, 2024. Updated Besponsa (inotuzumab ozogamicin) age requirement from 18 to 1 year of age or older.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.