Proposed Formulary Changes

Effective 7/1/2018 (unless otherwise noted)

Table 1: Summary of Medicaid PDL proposed designation as **Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Steglatro	Ertugliflozin	Tablet	5 mg, 15 mg		Approved
Segluromet	Ertugliflozin and metformin HCl	Tablet	2.5 mg/500 mg, 2.5 mg/ 1000 mg, 7.5 mg/500 mg, 7.5 mg/1000 mg		Approved
Kosher Prenatal Plus	Prenatal vitamin with iron carbonyl	Tablet	30-1 mg		Approved

Table 2: Summary of Medicaid PDL proposed designation as **Non-Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Ecoza	Econazole Nitrate	Cream	1%	Grandfather existing utilizers	Approved
Clotrimazole - Betamethasone	Clotrimazole/ betamethasone dipropionate	Lotion	1-0.05%	Grandfather existing utilizers	Approved
Benzamycin	Erthyromycin/ benzoyl peroxide gel	Gel	5-3%	Grandfather existing utilizers	Approved
Naprosyn	Naproxen	Suspension	125 mg/ 5 mL	Grandfather existing utilizers	Approved
Migranal	Dihydroergotamine mesylate	Nasal Spray	4 mg/ mL	Grandfather existing utilizers	Approved

New Drugs

Reviewed for P&T Meeting March **22**, 2018

Steglatro (ertugliflozin)

Therapeutic Class: Sodium-glucose cotransporter 2 (SGLT2) Inhibitor
FDA indication: Diabetes mellitus, type 2
Formulary Recommendations: Preferred
Rationale: Based on the data presented, Ertugliflozin is an effective therapy for reduction of blood sugar levels in patients diagnosed with Type 2 Diabetes Mellitus. Ertugliflozin is less costly than other SGLT2 medications currently approved for this indication that are on the preferred formulary. However, there are currently no head to head trials comparing the efficacy and safety of the Ertugliflozin to any of the other SGLT2 Inhibitors. Overall, it is comparable to other antidiabetic agents in efficacy and safety while providing significant cost savings when compared with the other SGLT2 inhibitors in its class. As a result, Steglatro should become the preferred class agent for SGLT2 inhibitors as its cost savings outweigh the savings of the rebate.
P&T Decision: Approved

Vosevi (sofosbuvir, velpatasvir, and voxilaprevir)

Therapeutic Class: Nucleotide analog NS5B polymerase inhibitor, NS5A inhibitor, NS3/4A protease inhibitor
FDA indication: Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection
Formulary Recommendations: Non-preferred
Rationale: New drug for Hepatitis C without cirrhosis or with compensated cirrhosis was reviewed. Vosevi's package insert, clinical trials and place on guidelines from American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) was reviewed. Based on other viable options that are currently preferred for treatment it was recommended to place medication in non-preferred category of coverage. It was determined that no policy needed at this time due to variety of other available drug options with existing polices.
P&T Decision: Approved

Idhifa (enasidenib)

Therapeutic Class: Isocitrate dehydrogenase-2 inhibitor
FDA indication: Adults with relapsed or refractory acute myeloid leukemia (AML) with isocitrate dehydrogenase (IDH)-2 mutation
Formulary Recommendations: Non-preferred
Rationale: Idhifa is the first agent approved for the treatment of IDH2 mutation-positive relapsed or refractory AML. The 2017 NCCN Clinical Practice Guidelines in Oncology for AML recommend a cytarabine-containing chemotherapy regimen, hypomethylating agent +/- sorafenib, or enrollment in a clinical trial for patients with relapsed or refractory AML. Idhifa has currently not been evaluated for inclusion in the NCCN guidelines. Idhifa is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.
P&T Decision: Approved

Mylotarg (gemtuzumab ozogamicin)

Therapeutic Class: CD33-directed antibody-drug conjugate
FDA indication: Newly-diagnosed CD33-positive acute myeloid leukemia; Relapsed or refractory CD33-positive AML in adults in pediatric patients 2 years and older
Formulary Recommendations: Non-preferred
Rationale: Mylotarg was originally approved by the FDA in 2000 and withdrew from the market after trials demonstrating lack of efficacy and increased safety concerns. New FDA approval includes a lower recommended dose, new dosing regimen, and approval for use in a new patient population. The 2017 NCCN Clinical Practice Guidelines in Oncology for AML have not been updated to include Mylotarg. Mylotarg is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.
P&T Decision: Approved

Besponsa (inotuzumab ozogamicin)

Therapeutic Class: CD22-directed antibody-drug conjugate
FDA indication: Adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Formulary Recommendations: Non-preferred
Rationale: Besponsa is the second agent FDA approved for relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The 2017 NCCN Clinical Practice Guidelines in Oncology for ALL recommend enrollment in clinical trial with Besponsa for patients with relapsed or refractory ALL. Besponsa is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.
P&T Decision: Approved

Nerlynx (Neratinib)

Therapeutic Class: Kinase inhibitor
FDA indication: Extended adjuvant treatment of adult patients with early state HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy
Formulary Recommendations: Non-preferred
Rationale: Nerlynx is the first agent approved for the extended adjuvant treatment of HER2-positive breast cancer following adjuvant therapy with Herceptin. Clinicals showed that patients with early stage HER2-positive breast cancer receiving treatment with Nerlynx for 12 months following therapy with Herceptin improved iDFS at 2 years compared with placebo. Nerlynx is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.
P&T Decision: Approved

Haegarda (C1 inhibitor (Human))

Therapeutic Class: C1 esterase inhibitor
FDA indication: Hereditary angioedema
Formulary Recommendations: Preferred; previously approved via e-vote 9/8/2017
Rationale: New drug for routine prophylaxis to prevent HAE attack was reviewed. Based on drug's clinical trials, package insert, and recommendations from professional society, it was determined that medication can be a viable option for our population. Preferred drug status is recommended.
P&T Decision: Approved

Kymriah (tisagenlecleucel)

Therapeutic Class: CD19-directed genetically modified autologous T cell immunotherapy
FDA indication: B-cell precursor acute lymphoblastic leukemia
Formulary Recommendations: Non-preferred; previously approved via e-vote on 11/1/2017, update 1/31/2018
Rationale: The first FDA approved CAR-T cell autologous immunotherapy was approved and reviewed for policy purposes. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. Healthcare facility or provider must be enrolled in the Kymriah REMS and has to have training on the management of cytokine release syndrome (CRS) and neurological toxicities.
P&T Decision: Approved

Mavyret (glecaprevir and pibrentasvir)

Therapeutic Class: NS3/4A protease inhibitor, NS5A inhibitor
FDA indication: Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection
Formulary Recommendations: Preferred; previously approved via e-vote 12/5/2017
Rationale: New drug for Hepatitis C without cirrhosis or with compensated cirrhosis was reviewed. Criteria for Mavyret was written based on package insert, clinical trials and guidelines from American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Based on shorter treatment period and a broad genotype coverage it was recommended to place medication in preferred category of coverage.
P&T Decision: Approved

Siliq (brodalumab)

Therapeutic Class: Human interleukin-17 receptor A (IL-17RA) antagonist
FDA indication: Plaque Psoriasis
Formulary Recommendations: Non-preferred; previously approved via e-vote 5/17/2017
Rationale: New drug for Plaque Psoriasis was reviewed. Criteria for Siliq are written based on trials data from drug's package insert and guideline consensus for the plaque psoriasis. Non-preferred drug status is recommended.
P&T Decision: Approved

Tremfya (guselkumab)

Therapeutic Class: Interleukin-23 inhibitor
FDA indication: Plaque Psoriasis
Formulary Recommendations: Non-preferred; previously approved via e-vote 11/8/2017
Rationale: New drug for Plaque Psoriasis was reviewed. Criteria for Tremfya are written based on trials data from drug's package insert and evidence-based guidelines from American Academy of Dermatology. Criteria aligned with existing drug criteria for Plaque Psoriasis. Non-preferred drug status is recommended.
P&T Decision: Approved

Pharmacy &Therapeutics Committee Summary Review
Steglatro® (Ertugliflozin) – Merck

Prepared by: Mark Pierce

Presentation Date: March 8, 2018

Therapeutic Class: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor

FDA Approval Date: December 20, 2017

FDA Indication: Diabetes mellitus, type 2

Comparable Formulary Products: Invokana® (Canagliflozin), Farxiga® (Dapagliflozin), Jardiance® (Empagliflozin)

Proposed Designation & Rationale
Recommendation: Preferred
Clinical Implications/Place in Therapy: Based on the data presented, Ertugliflozin is an effective therapy for reduction of blood sugar levels in patients diagnosed with Type 2 Diabetes Mellitus. Ertugliflozin is less costly than other SGLT2 medications currently approved for this indication that are on the preferred formulary.[12-15] However, there are currently no head to head trials comparing the efficacy and safety of the Ertugliflozin to any of the other SGLT2 Inhibitors. Overall, it is comparable to other antidiabetic agents in efficacy and safety while providing significant cost savings when compared with the other SGLT2 inhibitors in its class.[6-10] As a result, Steglatro should become the preferred class agent for SGLT2 inhibitors as its cost savings outweigh the savings of the rebate.

Clinical Pharmacology:
Ertugliflozin is a Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor. SGLT2 is responsible for regulating reabsorption of filtered glucose from the tubular lumen. Inhibition of this transporter leads to reduction of filtered glucose reabsorption and lowering of renal threshold for glucose result in increased urinary excretion of glucose, thereby reducing plasma glucose concentrations.

Notable Pharmacokinetics:

- Absorption:
  - T_{max}: 1 hour (fasting); 2 hours (administered with high-fat, high-calorie meal).
  - Bioavailability: ~100%
- Distribution:
  - Volume of distribution: 85.5 L
  - Protein binding: 93.6%
- Metabolism:
  - Primarily by UGT1A9 and UGT2B7-mediated O-glucuronidation to metabolites that are inactive at clinically relevant concentrations; CYP-mediated metabolism is minimal
- Elimination:
  - Half-life: 16.6 hours
  - Urine excretion 40.9%
  - Fecal excretion: 50.2%

Efficacy:

VERTIS SITA2 Trial[6]	
Trial Design/ Population	Randomized, double-blind, placebo-controlled Patients age 18+ with Type 2 diabetes mellitus who were receiving treatment with metformin and Sitagliptan at a stable dose for ≥8 weeks that had an HbA1c level of 7.0-10.5%
Groups	Ertugliflozin 5 mg/day, Ertugliflozin 15 mg/day, or placebo
Outcomes	• *Primary efficacy endpoint*: Change From Baseline in Hemoglobin A1C at Week 26, • *Secondary efficacy endpoints*: Change From Baseline in Fasting Plasma Glucose, Change From Baseline in Body Weight, Percentage of Participants With an A1C <7%, Change From Baseline in Sitting Systolic and Diastolic Blood Pressure, Change From Baseline in HOMA-%β, 20.Change From Baseline in EQ-5D-3L Questionnaire Score, • *Safety endpoints*: Percentage of Participants Experiencing An Adverse Event, percentage of Participants Discontinuing Study Treatment Due to an AE, Percentage of Participants Receiving Glycemic Rescue Medication, Time to Initiation of Glycemic Rescue
Results	• Significantly greater reductions in HbA1c from baseline were seen in the Ertugliflozin groups relative to the placebo group (placebo-adjusted least squares [LS] means [95% CI] HbA1c changes at Week 26: −0.7% [−0.9, −0.5] and −0.8% [−0.9, −0.6], respectively; P <.001 for both comparisons) • The odds of having HbA1c <7.0% (53 mmol/mol) at Week 26 were significantly greater in the Ertugliflozin groups vs the placebo group (both P < .001) • The rates of serious AEs and AEs leading to discontinuation were low and similar across treatment groups. No deaths were reported during the treatment period. The observed incidence of drug-related AEs was higher in the Ertugliflozin groups compared with the placebo group, largely the result of drug-related AEs were associated with genital mycotic infections (in women on Ertugliflozin 5mg at 52 weeks 12.0% versus 1.9% in placebo) (in men on Ertugliflozin 5mg at 52 weeks 4.9% versus 0% in placebo)
VERTIS RENAL Trial[7]	
Trial Design/ Population	Randomized, double-blind, placebo-controlled trial Patients age 25+ with Type 2 diabetes mellitus with Stage 3 chronic kidney disease who have inadequate control on antihyperglycemic therapy excluding metformin, rosiglitazone, and other SGLT2 Inhibitors.
Groups	Ertugliflozin 5 mg/day, Ertugliflozin 15 mg/day, or matching 5/10 mg placebo
Outcomes	• *Primary efficacy endpoint*: Change From Baseline in A1C at Week 26 - Excluding Rescue Approach • *Secondary efficacy endpoint*: Change From Baseline in Body Weight at Week 26, Change From Baseline in Sitting Systolic Blood Pressure, Change From Baseline in FPG, Percentage of Participants With A1C <7.0% • *Safety endpoints*: Percentage of Participants Who Experienced an Adverse Event, Percentage of Participants Who Discontinued Study Treatment Due to an AE,
Results	• No statistically significant mean changes from baseline in A1C were observed at week 26 (– 0.2% (95% CI – 0.5, 0.1) and – 0.4% (95% CI – 0.6, – 0.1) in the Ertugliflozin 5 mg and 15 mg groups, respectively). • However, metformin, which was used by approximately 17% of patients, modified the primary endpoint response. It is possible that patients self-medicated based on finger-stick glucose measurements, causing the results to be skewed as an unexpected reduction in the placebo group A1C was observed. • Greater reductions in body weight were observed for Ertugliflozin 5 mg and 15 mg versus placebo (p<0.001 for both comparisons). • There were also small reductions in SBP that were found insignificant for Ertugliflozin 5 mg and 15 mg versus placebo (p=0.451, p=0.072) in the Ertugliflozin 5 mg and 15 mg groups, respectively).

	• The incidence of renal-function- related AEs was low overall and more frequent in the Ertugliflozin groups than in the placebo group. Of the 11 Ertugliflozin-treated patients Ertugliflozin 5 mg, n = 7; Ertugliflozin 15 mg, n = 4) who experienced a hypovolemia AE by week 52, 18.2% were C 75 years of age (vs 21.6% of study participants overall), 81.8% were taking diuretics (vs 50.5% in the study overall), and 72.7% were in the stage 3A CKD cohort (vs 66% of patients in the study overall).
VERTIS SU Trial[8]	
Trial Design/ Population	Randomized, multicenter, double-blind, placebo-controlled trial Patients with Type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy.
Groups	Ertugliflozin 5 mg/day, Ertugliflozin 15 mg/day, or glimepiride titrated from 1 mg up to 6 or 8 mg QD
Outcomes	• *Primary efficacy endpoint*: Change from Baseline in Hemoglobin A1C at Week 52 • *Secondary efficacy endpoint*: Change from Baseline in Body Weight, •Change from Baseline in Systolic Blood Pressure • *Safety endpoints*: Number of Participants Experiencing An Adverse Event, Percentage of Participants Who Discontinued Study Treatment Due to an AE, Number of Participants with an Adverse Event of Symptomatic Hypoglycemia
Results	• Significant reductions from baseline in HbA1c were observed in all treatment groups. The least squares (LS) mean HbA1c changes (95% CI) from baseline at week 52 were - 7.0 (- 7.9, - 6.0), - 6.1 (- 7.1, - 5.1), and - 8.1 (- 9.0, - 7.1) mmol/mol (- 0.6% [- 0.7, - 0.5], - 0.6% [- 0.6, - 0.5], and - 0.7% [- 0.8, - 0.7]) in the ertugliflozin 15 mg, Ertugliflozin 5 mg, and glimepiride groups, respectively • Greater reductions from baseline in body weight were observed at week 52 in the Ertugliflozin groups compared with glimepiride . The LS mean changes (95% CI) in body weight from baseline at week 52 were - 3.4 kg (- 3.7, - 3.0), - 3.0 kg (- 3.3, - 2.6), and 0.9 kg (0.6, 1.3) in the Ertugliflozin 15 mg, Ertugliflozin 5 mg, and glimepiride groups, respectively • The incidence of symptomatic hypoglycemia was lower in the Ertugliflozin groups compared with the glimepiride group (Table 3). Severe hypoglycemia was reported in 1 (0.2%), 1 (0.2%), and 10 (2.3%) patients in the Ertugliflozin 15 mg, Ertugliflozin 5 mg, and glimepiride groups, respectively. • Seven deaths (1 [0.2%], 5 [1.1%], and 1 [0.2%] in the Ertugliflozin 15 mg, Ertugliflozin 5 mg, and glimepiride groups, respectively) were reported during the study (including the treatment and post-treatment periods). None of the deaths was considered by the investigators to be drug-related, and there was no pattern in causes of deaths as determined by the reported AE terms.
VERTIS SITA Trial[9]	
Trial Design/ Population	Randomized, multicenter, double-blind, placebo-controlled trial Patients with Type 2 diabetes mellitus with inadequate glycemic control on diet and exercise alone.
Groups	Ertugliflozin 5 mg QD and sitagliptin 100 mg QD, Ertugliflozin 15 mg QD and sitagliptin 100 mg QD, or placebo.
Outcomes	• *Primary efficacy endpoint*: Change From Baseline in Hemoglobin A1C (HbA1C) at Week 26 • *Secondary efficacy endpoint*: Change From Baseline in Body Weight at Week 26, Change From Baseline in Sitting Systolic and Diastolic Blood Pressure, Change From Baseline in FPG, Change From Baseline in 2-hour Post-Meal Glucose, Percentage of Participants With A1C <7.0% • *Safety endpoints*: Percentage of Participants Who Experienced an Adverse Event, Percentage of Participants Who Discontinued Study Treatment Due to an AE.
Results	• Both ertugliflozin/sitagliptin treatments provided significant reductions from baseline in HbA1c compared with placebo [least squares mean HbA1c change (95% CI) from baseline was - 0.4% (- 0.7, - 0.2), - 1.6% (- 1.8, - 1.4), and - 1.7% (- 1.9, - 1.5) for placebo, E5/S100, and E15/S100, respectively • Significant reductions in fasting plasma glucose, 2-h post-prandial glucose, body weight, and systolic blood pressure were observed with both ertugliflozin/sitagliptin groups compared with placebo.

	• The incidence of adverse events (AEs) was similar across the groups. The incidences of the pre-specified AEs of urinary tract infection, genital mycotic infection, symptomatic hypoglycemia, and hypovolemia were low and not meaningfully different across groups.
VERTIS FACTORIAL Trial[10]	
Trial Design/ Population	Randomized, multicenter, double-blind, placebo-controlled trial Patients age ≥18 with Type 2 diabetes mellitus with inadequate glycemic control on Metformin monotherapy at a stable dose for ≥8 weeks.
Groups	Ertugliflozin 5 mg QD and sitagliptin 100 mg QD, Ertugliflozin 15 mg QD and sitagliptin 100 mg QD, sitagliptin 100 mg QD, Ertugliflozin 15 mg QD, or Ertugliflozin 5 mg QD.
Outcomes	• *Primary efficacy endpoint*: Change From Baseline in Hemoglobin A1C (HbA1C) at Week 26 • *Secondary efficacy endpoint*: Change From Baseline in Body Weight at Week 26, Change From Baseline in Sitting Systolic Blood Pressure, Change From Baseline in FPG, Change From Baseline in Static Beta-Cell Sensitivity to Glucose Index, Percentage of Participants With A1C <7.0% • *Safety endpoints*: Percentage of Participants Who Experienced an Adverse Event, Percentage of Participants Who Discontinued Study Treatment Due to an AE.
Results	• HbA1c reductions from baseline were greater with E5/S100 (−1.5%) and E15/S100 (−1.5%) than with individual agents (−1.0%, −1.1% and −1.1% for E5, E15 and S100, respectively; P < .001 for all comparisons) • Fasting plasma glucose reductions were significantly greater with E5/S100 and E15/S100 compared with individual agents. Body weight and systolic blood pressure (SBP) significantly decreased with E5/S100 and E15/S100 vs S100 alone. • Genital mycotic infections were more common among ertugliflozin-treated patients compared with those treated with S100. Incidences of symptomatic hypoglycemia and adverse events related to hypovolemia or urinary tract infection were similar among groups.

Conclusion: Steglatro (Ertugliflozin) is an effective and reasonably safe agent for the management of high blood sugar in patients with Type 2 Diabetes Mellitus.

Ongoing Clinical Trials:

- NCT01986881 – Study of the cardiovascular outcomes following treatment with ertugliflozin in participants with type 2 diabetes mellitus (T2DM) and established vascular disease.
- NCT03416270 –Study to elucidate the mechanisms whereby the SGLT2i "ertugliflozin" modifies cardiorenal interactions that regulate fluid volume and neuro-hormonal activation in patients with type 2 diabetes and heart failure (T2D-HF).

Contraindications:

- History of serious hypersensitivity reaction to Ertugliflozin or any component of the formulation
- Severe renal impairment
- End-stage renal disease, or dialysis

Warnings/Precautions:

- Bone fractures:
  - An increased incidence of bone fractures has been observed with other sodium-glucose cotransporter 2 (SGLT2) inhibitors in some clinical trials. However, meta-analyses of trial data for canagliflozin, dapagliflozin, and empagliflozin have not demonstrated increased risk of fracture overall.[1,2] One placebo-controlled trial with ertugliflozin did not show changes in bone mineral density (BMD) after 26 weeks, but additional longer-term data are required to more accurately define fracture risk.[3]
- Genital mycotic infections:
  - Patients with a history of these infections or uncircumcised males are at greater risk.
- Hypotension:
  - Patients with renal impairment, elderly, patients on other antihypertensives, or those with low systolic blood pressure are at increased risk.

- Assess volume status prior to initiation in patients at risk of hypotension and correct if depleted; monitor for signs and symptoms of hypotension after initiation.
- Ketoacidosis:
  - Before initiating treatment, consider risk factors that may predispose to ketoacidosis.[4]
  - The American Association of Clinical Endocrinologists and American College of Endocrinology recommend considering withholding of SGLT2 inhibitors for at least 24 hours prior to events that may precipitate diabetic ketoacidosis[4], while others have suggested withholding for 3 to 5 days.[5]
- Lipid abnormality:
  - May cause dose-related LDL-C elevation; monitor LDL-C and treat as needed.
- Lower limb amputation:
  - Prior to initiation consider risk factors for amputation including prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.
  - Counsel patients about the importance of preventative foot care. Monitor for signs and symptoms of new infection (including osteomyelitis), new pain or tenderness, or sores/ulcers involving the lower limbs.
- Renal effects:
  - Prior to initiation, consider risk factors for acute kidney injury (eg, hypovolemia, chronic renal insufficiency, heart failure, use of concomitant medications [eg, diuretics, ACE inhibitors, angiotensin receptor blockers, NSAIDs]).
  - Assess renal function prior to initiation and periodically during treatment.
- Urinary tract infection:
  - Monitor for signs and symptoms of UTI and treat as needed.

Drug Interactions:
- *Sulfonylureas* – Consider a decrease in sulfonylurea dose when initiating therapy with a SGLT2 inhibitor
- *Insulins* – Consider a decrease in insulin dose when initiating therapy with a SGLT2 inhibitor

Common Adverse Effects:
- Common (≥ 2%)
  - Genital candidiasis (females: 9% to 12%; males: 4%)
  - Headache
  - Hypoglycemia
  - Weight loss
  - Urinary frequency
  - Vulvovaginal pruritus
  - Back pain
  - Nasopharyngitis
  - Increased thirst

Safety:
- *Sound Alike Look Alike:* None
- *REMs Program Requirement:* None
- *Known safety issues (ISMP safety alerts):* High alert
- *Pregnancy*: May cause fetal harm in second and third trimesters
- *Breastfeeding*: Unknown if present in breastmilk, breastfeeding during therapy is not recommended by the manufacturer

Dosage/Administration:
- Initial dose: 5mg once daily with or without food for one week then increase
- Maintenance dose: May increase dose to maximum of 15mg once daily with or without food
- Hepatic impairment (mild or moderate): No dosage adjustment necessary
- Hepatic impairment (severe): Use is not recommended (has not been studied)
- Renal impairment (CrCl ≥60 mL/min): No dose adjustment necessary; not recommended in CrCl 30-60 mL/min.

Special Drug Monitoring: Monitor HbA_{1C}, renal function, volume status, and signs & symptoms of metabolic acidosis

Handling and Preparation: No special instructions.

Financial Impact:

- *Prevalence of diabetes*
  - 29.1 million people (9.3%) of the U.S. population have diabetes (diagnosed and undiagnosed)[11]
  - Estimated that 86 million (37%) of the U.S. population (≥ 20 years) have prediabetes[11]
  - Estimated total (direct and indirect) diabetes cost at $245 billion[11]
  - 7th leading cause of death in the U.S.[11]
- *Acquisition cost and annual budget impact*
  - Monthly cost: $321.84 (either strength)
- *Manage-care costs*
  - Potential increased risk for UTI, lower limb infections, and metabolic acidosis
- *Pharmacoeconomic data*
  - None published

Drug	Steglatro (Ertugliflozin)[12]	Invokana (Canagliflozin)[13]	Farxiga (Dapagliflozin)[14]	Jardiance (Empagliflozin)[15]
AWP (30 day supply)	$321.84	$557.50	$557.45	$557.94
Annual cost	$3,861.84/yr	$6,690/yr	$6,689.40/yr	$6,695.28/yr

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Pharmacy &Therapeutics Committee Summary Review

Besponsa® (Inotuzumab Ozogamicin) – Wyeth Pharmaceuticals Inc

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 3/8/2017

Therapeutic Class: CD22-directed antibody-drug conjugate

FDA Approval Date: 8/17/2017

FDA Indication: Adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia

Comparable Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred
Clinical Implications/ Place in Therapy: Besponsa is the second agent FDA approved for relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The 2017 NCCN Clinical Practice Guidelines in Oncology for ALL recommend enrollment in clinical trial with Besponsa for patients with relapsed or refractory ALL. Besponsa is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Besponsa™ (inotuzumab ozogamicin) intravenous injection Pfizer, Inc.

INDICATION

Besponsa (inotuzumab ozogamicin) is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) (Besponsa prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Besponsa (inotuzumab ozogamicin) was approved by the FDA on August 17, 2017 with a review designation of 1P (FDA, 2017a; FDA, 2017b). Besponsa (inotuzumab ozogamicin) is a new molecular entity that underwent priority review and was granted breakthrough therapy and orphan drug designations (FDA, 2017b). An agent may qualify for a breakthrough therapy program if it treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoints compared with available therapies (FDA, 2014).

DRUG SUMMARY

Besponsa (inotuzumab ozogamicin)	
Place in Therapy	• Besponsa is the second agent FDA-approved to treat adults with relapsed or refractory B-cell precursor ALL. • The 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for ALL recommend enrollment in a clinical trial, TKI ± chemotherapy or corticosteroids ± HSCT (Ph-positive ALL only), chemotherapy ± HSCT, inotuzumab ozogamicin (Besponsa), blinatumomab (Blincyto), or tisagenlecleucel (Kymriah) for patients with relapsed or refractory ALL.
Efficacy	• Approval for Besponsa was based on an open-label, multinational, phase III, active-controlled trial evaluated the efficacy and safety of Besponsa in relapsed or refractory CD-22 positive, B-cell ALL compared to standard chemotherapy. • Patients receiving Besponsa had a significantly higher rate of CR/CRi compared to standard chemotherapy.
Safety	• Boxed Warnings: hepatotoxicity, including life-threatening hepatic VOD, has been observed during or following treatment with Besponsa or following a HSCT after completion of treatment; and increased post-HSCT non-relapse mortality. • Warnings/Precautions: myelosuppression, infusion-related reactions, QT prolongation, and embryo-fetal toxicity. • Adverse Events (≥ 25%): infection, thrombocytopenia, anemia, leukopenia, febrile neutropenia, headache, hemorrhage, nausea, abdominal pain, fatigue, pyrexia, and increased transaminases.

ALL = acute lymphoblastic leukemia
CD = cluster of differentiation
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
FDA = Food and Drug Administration
HSCT = hematopoietic stem cell transplant
NCCN = National Comprehensive Cancer Network
Ph = Philadelphia chromosome
TKI = tyrosine kinase inhibitor
VOD = veno-occlusive disease

CLINICAL PHARMACOLOGY

Mechanism of Action

Inotuzumab ozogamicin is a cluster of differentiation (CD) 22-directed antibody-drug conjugate (ADC) (Besponsa prescribing information, 2017). Inotuzumab, which recognizes human CD22, is covalently attached to the cytotoxic agent N-acetyl-gamma-calicheamicin. The ADC binds to CD22-expressing tumor cells, which causes the internalization of the ADC-CD22 complex. Following internalization, N-acetyl-gamma-calicheamicin is released and, once activated, induces double-strand deoxyribonucleic acid (DNA) breaks, subsequently inducing cell cycle arrest and apoptotic death.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of inotuzumab ozogamicin

Route of Administration	Volume of Distribution	Protein Binding	Metabolism	$T_{1/2}$
Intravenous	97%*	97%*	Nonenzymatic reduction*	12.3 hours

* Inactive N-acetyl-gamma-calicheamicin only

$T_{1/2}$ = elimination half-life

T_{max} = time to maximum plasma concentration

(Besponsa prescribing information, 2017)

Pharmacogenomics

No pharmacogenomics data are available at this time for inotuzumab ozogamicin.

CLINICAL EFFICACY

Table 2: Efficacy of Besponsa (inotuzumab ozogamicin) in the Treatment of Relapsed or Refractory B-cell ALL

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Kantarjian, 2016 Evidence Level Ib **Besponsa*** (n = 109) vs. **Investigator's Choice of Chemotherapy†** (n = 109)	(N = 218) **Study Design:** Open-label, multinational, randomized, phase III, active-control trial **Objective:** To assess the efficacy and safety of Besponsa as first or second salvage treatment in adults with relapsed or refractory B-cell ALL **Primary Endpoints:** • CR + CRi • OS **Secondary Endpoint:** Rate of subsequent HSCT	**Inclusion Criteria:** • ≥ 18 years of age (median age 47 years, 67% male, 67% on first salvage therapy) • ECOG ≤ 2‡ • Relapsed or refractory, CD22-positive, Ph-positive or Ph-negative ALL • Scheduled to receive first or second salvage treatment **Exclusion Criteria:** • Chemotherapy < 2 weeks before randomization • Allogenic HSCT ≤ 4 months before randomization	See below

Endpoint	Besponsa (n = 109) (95% CI)	Chemotherapy (n = 109) (95% CI)	Between-Group Difference (97.5% CI)	HR (97.5% CI)	p-value
CR + CRi	80.7% (72.1 to 87.7)	29.4% (21.0 to 38.8)	51.4% (38.4 to 64.3)	—	< 0.001
CR	35.8% (26.8 to 45.5)	17.4% (10.8 to 25.9)	18.3% (5.2 to 31.5)	—	0.002
CRi	45.0% (35.4 to 54.8)	11.9% (6.5 to 19.5)	33.0% (20.3 to 45.8)	—	< 0.001
OS	7.7 months (6.0 to 9.2)	6.7 months (4.9 to 8.3)	—	0.77 (0.58 to 1.03)	NS
Subsequent HSCT	41%	11%	—	—	< 0.001

Safety

- The most common adverse events (≥ 15%) in both treatment arms were the following: thrombocytopenia, neutropenia, anemia, nausea, febrile neutropenia, and neutropenia. For all of these adverse events, the rates were higher in the chemotherapy arm compared with the Besponsa arm.
- The Besponsa arm experienced a higher rate of VOD compared with the chemotherapy arm (11% vs. 1%). The majority of patients in the Besponsa arm who developed VOD did so following HSCT.

Comments/Study Limitations: In both treatment arms, the majority of patients who achieved CR or CRi did so by at the end of the first cycle.

Conclusions: Compared to standard chemotherapy, Besponsa had significantly higher rates of CR and CRi as well as a higher rate of HSCT following treatment in patients with B-cell ALL. However, Besponsa did not significantly improve OS compared to chemotherapy. In addition, Besponsa was generally associated with lower rates of adverse events, with the notable exception of VOD.

* Initial dosing regimen was 0.8 mg/m^2 IV on day 1 of each cycle then 0.5 mg/m^2 IV on day 8 and day 15; once CR or CRi was achieved, the day 1 cycle was reduced to 0.5 mg/m^2. Patients received up to six cycles.

† Investigator's choice of chemotherapy was one of the following regimens: FLAG for up to four 28-day cycles (cytarabine 2 g/m^2 on day 1 through day 6 + fludarabine 30 mg/m^2 on day 2 through day 6 + granulocyte colony-stimulating factor 5 µg/kg per day or at the institutional standard dose); cytarabine 200 mg/m^2 on day 1 through day 7 + mitoxantrone 12 mg/m^2 on day 1 through day 3 for up to four 15-to-20 day cycles; high-dose cytarabine 3 g/m^2 every 12 hours for up to one 12-dose cycle

‡ ECOG performance status scale rates a patient's level of function from 0 to 5, where 0 = fully active, able to carry on all pre-disease performance without restriction and 5 = dead

ALL = acute lymphoblastic leukemia
CD = cluster of differentiation
CI = confidence interval
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
ECOG = Eastern Cooperative Oncology Group
FLAG = fludarabine + cytarabine + granulocyte colony-stimulating factor
HR = hazard ratio
HSCT = hematopoietic stem cell transplantation
IV = intravenous
NS = not significant
OS = overall survival
Ph = Philadelphia chromosome
VOD = veno-occlusive disease

(Kantarjian, 2016)

Boxed Warning

HEPATOTOXICITY, INCLUDING HEPATIC VENO-OCCLUSIVE DISEASE (VOD)

(ALSO KNOWN AS SINUSIDOIDAL OBSTRUCTION SYNDROME)

Hepatotoxicity, including life-threatening hepatic VOD, has been observed during or following treatment with Besponsa (inotuzumab ozogamicin) or following a hematopoietic stem cell transplant (HSCT) after completion of treatment (Besponsa prescribing information, 2017). The risk of VOD was higher in patients who underwent HSCT following Besponsa (inotuzumab ozogamicin) treatment, use of HSCT conditioning regimens containing two alkylating agents, and last total bilirubin level at least at the upper limit of normal before HSCT. Additional risk factors for VOD include ongoing or prior liver disease, prior HSCT, increased age, later salvage lines, and a greater number of Besponsa (inotuzumab ozogamicin) cycles. Patients should be monitored closely for signs and symptoms of VOD.

INCREASED RISK OF POST-HSCT NON-RELAPSE MORTALITY

Besponsa (inotuzumab ozogamicin) is associated with a higher rate of post-HSCT non-relapse mortality compared to chemotherapy (Besponsa prescribing information, 2017). The most common causes of non-relapse mortality include VOD and infections.

Warnings and Precautions

Myelosuppression

Myelosuppression has been observed in patients receiving Besponsa (inotuzumab ozogamicin) (Besponsa prescribing information, 2017). Complete blood counts should be monitored prior to each dose of Besponsa (inotuzumab ozogamicin), and patients should be monitored for signs and symptoms of myelosuppression during treatment with Besponsa (inotuzumab ozogamicin).

Infusion-Related Reactions

Infusion-related reactions have occurred in patients receiving Besponsa (inotuzumab ozogamicin) (Besponsa prescribing information, 2017). In the clinical trial, infusion-related reactions generally occurred during the first cycle of treatment shortly after the end of the Besponsa (inotuzumab ozogamicin) infusion and resolved spontaneously or following medical management. Patients receiving Besponsa (inotuzumab ozogamicin) should receive pretreatment with a corticosteroid, an antipyretic, and an antihistamine prior to the infusion. Patients should be monitored closely during and for at least one hour after the end of the infusion for signs and symptoms of infusion-related reactions.

QT Prolongation

Increases in QT interval have been observed in patients receiving Besponsa (inotuzumab ozogamicin) (Besponsa prescribing information, 2017). Besponsa (inotuzumab ozogamicin) should be administered cautiously in patients with a history of or predisposition for QT prolongation, patients receiving other QT-prolonging medications, and patients with electrolyte disturbances. Electrocardiograms and electrolytes should be obtained prior to the start of treatment, after the initiation of any QT-prolonging medication, and then periodically monitored as necessary during treatment.

Embryo-Fetal Toxicity

Based upon the mechanism of action and animal reproduction studies, Besponsa (inotuzumab ozogamicin) can cause embryo-fetal harm when administered to a pregnant woman (Besponsa prescribing information, 2017). Female patients with reproductive potential should utilize effective contraception during treatment with Besponsa (inotuzumab ozogamicin) and for at least eight months following the last dose of Besponsa (inotuzumab ozogamicin). Male patients with female partners of reproductive potential should utilize effective contraception during treatment with Besponsa (inotuzumab ozogamicin) and for at least five months following the last dose of Besponsa (inotuzumab ozogamicin).

Nursing Mothers

No data are available regarding the presence of inotuzumab ozogamicin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production (Besponsa prescribing information, 2017). Women are advised to not breastfeed during treatment with Besponsa (inotuzumab ozogamicin) and for at least two months after the last dose.

Pediatric Use

Safety and efficacy of Besponsa (inotuzumab ozogamicin) have not been established in pediatric patients (Besponsa prescribing information, 2017).

Geriatric Use

In the clinical trial, 18% of patients who received Besponsa (inotuzumab ozogamicin) were 65 years of age and older (Besponsa prescribing information, 2017). No differences in responses were identified between older and younger patients.

Drug Interactions

Table 3: Potential Drug Interactions with Inotuzumab Ozogamicin

Interacting Agent	Outcome	Recommendation
QT-prolonging agents or Torsades de Pointes-inducing agents	Increased risk of clinically significant QTc interval prolongation	Interacting agent should be discontinued or alternative concomitant drugs that do not prolong QT interval should be used
		If unable to avoid concomitant use, ECGs and electrolyte levels should be obtained prior to the start of treatment, after initiation of any QT-prolonging agent, and should be periodically monitored during treatment

ECG = electrocardiogram

(Besponsa prescribing information, 2017)

Adverse Events

Table 4: Adverse Events for Besponsa (inotuzumab ozogamicin) in ≥ 15% of Patients with Relapsed or Refractory B-cell Precursor ALL

Adverse Event	Besponsa (n = 164)	Investigator's Choice of Chemotherapy* (n = 143)
Infection	48%	76%
Thrombocytopenia	51%	61%
Neutropenia	49%	45%
Anemia	36%	59%
Leukopenia	35%	43%
Febrile neutropenia	26%	53%
Lymphopenia	18%	27%
Headache	28%	27%
Hemorrhage	33%	28%
Nausea	31%	46%
Abdominal pain	23%	23%
Diarrhea	17%	38%
Constipation	16%	24%
Vomiting	15%	24%
Hyperbilirubinemia	21%	17%
Fatigue	35%	25%
Pyrexia	32%	42%
Increased transaminases	26%	13%
Increased GGT	21%	8%

* Investigator's choice of chemotherapy was defined as FLAG, MXN/Ara-C, or HIDAC
FLAG = fludarabine + cytarabine + granulocyte colony-stimulating factor
HIDAC = high dose cytarabine
GGT = gamma-glutamyltransferase
MXN/Ara-C = mitoxantrone + cytarabine

(Besponsa prescribing information, 2017)

Table 5: Grade 3 or 4 Laboratory Abnormalities for Besponsa (inotuzumab ozogamicin) in ≥ 50% of Patients with Relapsed or Refractory B-cell Precursor ALL

Adverse Event	Besponsa (n = 161)	Investigator's Choice of Chemotherapy* (n = 142)
Decreased platelet count	76%	99%
Decreased hemoglobin	40%	70%
Decreased leukocytes	82%	98%
Decreased neutrophil count	86%	88%
Decreased absolute lymphocytes	71%	91%

* Investigator's choice of chemotherapy was defined as FLAG, MXN/Ara-C, or HIDAC
FLAG = fludarabine + cytarabine + granulocyte colony-stimulating factor
MXN/Ara-C = mitoxantrone + cytarabine
HIDAC = high dose cytarabine

(Besponsa prescribing information, 2017)

Immunogenicity

In clinical trials, 3% of patients who received Besponsa (inotuzumab ozogamicin) tested positive for anti-inotuzumab ozogamicin antibodies (Besponsa prescribing information, 2017). No patients tested positive for neutralizing anti-inotuzumab ozogamicin antibodies.

PRODUCT AVAILABILITY

Besponsa (inotuzumab ozogamicin) is available as a single-dose vial, which upon reconstitution and further dilution, delivers 0.9 mg of Besponsa (inotuzumab ozogamicin) (Besponsa prescribing information, 2017). Each carton contains one single-dose vial. Besponsa (inotuzumab ozogamicin) should be stored refrigerated at 2°C to 8°C (36°F to 46°F) protected from light. Besponsa (inotuzumab ozogamicin) launched on August 22, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

Besponsa (inotuzumab ozogamicin) is administered as a 60-minute infusion, with dosing based on the cycle and treatment response, as summarized in Table 6 (Besponsa prescribing information, 2017). For patients proceeding to HSCT, the recommended dose is two cycles of Besponsa (inotuzumab ozogamicin), and an additional cycle may be administered for patients who do not achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi). For patients who are not proceeding to HSCT, a maximum of six cycles may be administered. Premedication with a corticosteroid, an antipyretic, and an antihistamine should be administered. The dose of Besponsa (inotuzumab ozogamicin) should be modified based on adverse events such as a decrease in absolute neutrophil count and infusion-related reactions, with details of dose modifications provided in the prescribing information.

Table 6: Dosing Regimens for Cycle One and Subsequent Cycles Depending on Response to Treatment for Besponsa (inotuzumab ozogamicin)

	Day 1	Day 8 and Day 15
Cycle One		
Dose	0.8 mg/m^2	0.5 mg/m^2
Cycle Length	21 days to 28 days*	
Subsequent Cycles in Patients who have achieved a CR or CRi		
Dose	0.5 mg/m^2	0.5 mg/m^2
Cycle Length	28 days	
Subsequent Cycles in Patients who have not achieved a CR or CRi		
Dose	0.8 mg/m^2	0.5 mg/m^2
Cycle Length	28 days	

* Treatment duration can be extended to 28 days if the patient achieves CR or CRi and/or to allow recovery from toxicity
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
(Besponsa prescribing information, 2017)

APPROACHES TO TREATMENT

ALL, which is characterized by the proliferation of immature lymphoid cells in the blood, bone marrow, and other organs, is the most common form of childhood leukemia but accounts for only 20% of all adult leukemia cases (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2017). ALL is rare, with an estimated 5,790 new cases and an estimated 1,440 deaths in 2017 (National Cancer Institute [NCI], 2017). ALL is most common in children, teens, and young adults, with a median age of diagnosis of 15 years of age. However, despite this young median age of diagnosis, the highest rate of ALL deaths occurs in patients 65 years of age to 74 years of age, with a median age at death of 55 years of age. In addition, ALL is more common in Caucasians and Hispanics and is slightly more common in males.

The signs and symptoms of ALL are generally nonspecific and can include fatigue or lethargy, fevers, night sweats, weight loss, dyspnea, dizziness, infections, and easy bruising or bleeding (NCCN Guidelines, 2017). In addition, roughly 20% of patients may also present with lymphadenopathy, splenomegaly, and/or hepatomegaly.

Patients are diagnosed with ALL if they present with ≥ 20% lymphoblasts in bone marrow aspirate (NCCN Guidelines, 2017). Once diagnosed, ALL is subtyped based upon the immunophenotype of the cancer, specifically whether ALL develops from B-cells or T-cells as well as the maturity of the leukemia cells (American Cancer Society [ACS], 2016). B-cell lineage ALL is more common than T-cell lineage ALL and accounts for approximately 75% of adult ALL cases (NCCN Guidelines, 2017). Of the B-cell ALL subtypes, early precursor B-cell ALL accounts for an estimated 10% of cases, common B-cell ALL accounts for roughly 50% of cases, precursor B-cell ALL accounts for about 10% of cases, and mature B-cell ALL accounts for about 4% of cases (ACS, 2016).

In adults newly diagnosed with B-cell ALL, 60% to 90% of patients achieve CR with initial therapy (Kantarjian, 2016). Despite the high rate of CR with initial therapy, many patients will experience a relapse, and only 30% to 50% of patients have disease-free survival lasting three years or longer.

Several different genetic mutations and chromosomal abnormalities have been identified in ALL; however, only the breakpoint cluster region (BCR)-Abelson murine leukemia viral oncogene homolog 1 (ABL1) translocation, or Philadelphia chromosome (Ph), has FDA-approved targeted therapies (NCCN Guidelines®, 2017). Ph occurs in an estimated 25% of adult patients with ALL and is targeted by the tyrosine kinase inhibitors (TKIs) Sprycel (dasatinib), Gleevec (imatinib), Iclusig (ponatinib), Tasigna (nilotinib), and Bosulif (bosutinib).

Multiple prognostic factors have been identified which can be associated with favorable or unfavorable outcomes in ALL (ACS, 2016). Younger patients, patients with a lower white blood count (WBC) count (i.e., $< 30 \times 10^9$ WBCs/L for B-cell ALL and $< 100 \times 10^9$ WBCs/L for T-cell ALL) at diagnosis, patients with T-cell ALL, and patients who achieve CR within four weeks to five weeks of starting treatment have a better prognosis. Meanwhile, patients with mature B-cell ALL, translocations between chromosome 4 and chromosome 11, presence of an extra chromosome 8, a missing chromosome 7, and patients who do not achieve CR have a poorer prognosis. Prior to the development of targeted agents, the presence of Ph was associated with a poorer prognosis.

Of the antineoplastic agents currently available, only Besponsa (inotuzumab ozogamicin), Blincyto (blinatumomab), and Kymriah (tisagenlecleucel) are FDA-approved to treat relapsed or refractory B-cell precursor ALL (Prescribing information: Besponsa, 2017; Blincyto, 2017; Kymriah, 2017). However, Kymriah (tisagenlecleucel) is only approved in patients up to 25 years of age and involves the genetic modification of the patient's own T-cells (Kymriah prescribing information, 2017).

The 2017 NCCN Guidelines for ALL provide recommendations for relapsed or refractory ALL based upon whether or not patients are positive for Ph (NCCN Guidelines, 2017). For patients who are Ph-positive, the NCCN Guidelines® recommend any of the following: enrollment in a clinical trial; TKI ± chemotherapy or corticosteroids ± HSCT; blinatumomab (Blincyto) for patients with B-cell ALL after failure of two TKIs; inotuzumab ozogamicin (Besponsa) in patients with B-cell ALL who are intolerant or refractory to TKIs; or tisagenlecleucel (Kymriah) in patients with B-cell ALL who are ≤ 25 years of age and with refractory disease or at least two relapses and failure of two TKIs. The recommended TKIs are dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), imatinib (Gleevec), and ponatinib (Iclusig), and the choice of TKI depends on the specific Ph mutation profile.

For patients who are Ph-negative, the 2017 NCCN Guidelines recommend any of the following: enrollment in a clinical trial; chemotherapy ± HSCT; blinatumomab (Blincyto) in patients with B-cell ALL; inotuzumab ozogamicin (Besponsa) in patients with B-cell ALL; or tisagenlecleucel (Kymriah) in patients with B-cell ALL who are ≤ 25 years of age and with refractory disease or at least two relapses (NCCN Guidelines, 2017). The regimens recommended for Ph-negative ALL may also be considered in patients with Ph-positive ALL who are refractory to TKIs.

National Institute for Health and Care Excellence (NICE)

NICE recommends Blincyto (blinatumomab) as a treatment option for Ph-negative relapsed or refractory precursor B-cell ALL (NICE, 2017a). In addition, Iclusig (ponatinib) is recommended for the treatment of Ph-positive relapsed or refractory ALL when there is resistance or intolerance to Sprycel (dasatinib) and subsequent treatment with Gleevec (imatinib) is not clinically appropriate, or the T315I gene mutation is present. NICE is currently evaluating Besponsa (inotuzumab ozogamicin) for the treatment of relapsed or refractory ALL, and the expected publication date is September 27, 2017 (NICE, 2017b).

Table 7: Advantages and Disadvantages of Agents for Relapsed/Refractory B-cell Precursor ALL

Drug	Advantages	Disadvantages
Besponsa (inotuzumab ozogamicin)	• Short infusion time • No hospitalization required during infusion • Dosed once weekly • Appears to have better improvement in CR/CRi than Blinctyo when compared with chemotherapy	• Boxed warnings for hepatotoxicity, including VOD, and increased risk of post-HSCT non-relapse mortality • Warnings for infusion-related reactions and QT interval prolongation
Blincyto (blinatumomab)	• Approved for treatment in both adults and children • No drug-drug interactions reported	• 24 hour or 48 hour infusion time • Hospitalization required during first nine days of the first cycle and first two days of the second cycle • Boxed warnings for cytokine release syndrome and neurological toxicities • Warnings for infections, tumor lysis syndrome, leukoencephalitis, and pancreatitis

ALL = acute lymphoblastic leukemia
CR = complete remission
CRi = complete remission with incomplete hematologic recovery
HSCT = hematopoietic stem cell transplant
VOD = veno-occlusive disease

FORMULARY CONSIDERATIONS

Besponsa (inotuzumab ozogamicin) is the second agent FDA approved to treat adults with relapsed or refractory B-cell precursor ALL. Approval of Besponsa (inotuzumab ozogamicin) was based on an open-label, multinational, phase III, active-controlled trial, which demonstrated a significantly higher rate of CR and CRi compared to standard chemotherapy. Besponsa (inotuzumab ozogamicin) has boxed warnings for hepatotoxicity, including VOD, and increased risk of post-HSCT non-relapse mortality. In addition, Besponsa (inotuzumab ozogamicin) is associated with a high rate of adverse events, with the most common (i.e., ≥ 30%) being infection, thrombocytopenia, neutropenia, anemia, leukopenia, hemorrhage, nausea, pain, fatigue, and pyrexia.

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National Comprehensive Cancer Network. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia, V.3.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed September 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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DRUG MONOGRAPH PREPARED BY:

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October 18, 2017

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Pharmacy &Therapeutics Committee Summary Review
Haegarda (C1 Inhibitor (Human)) – CSL Behring LLC

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2018

Therapeutic Class: C1 esterase inhibitor

FDA Approval Date: 6/22/2017

FDA Indication: Hereditary angioedema

Comparable Products: Ruconest (non-preferred)

Proposed Designation & Rationale

Recommendation: Preferred

- For initial authorization:
  - Member must be 12 years of age or older, and medication is being used for routine prophylaxis to prevent HAE attacks (NOT for treatment of acquired angioedema); AND
  - Medication prescribed by or in consultation with a provider specializing in allergy, immunology, or hematology; AND
  - Member must have a confirmed diagnosis of HAE as one of the following:
    - Type 1 HAE documented in chart notes with ALL of the following (Note: tests listed below must be repeated for confirmation of diagnosis):
      - Low levels (below the limits of the laboratory's normal reference range) of C4, C1-INH antigenic protein and C1-INH functional level; AND
      - Positive family history of angioedema OR earlier age of onset (before age 30) with normal C1q antigenic protein level;
    - Type 2 HAE documented in chart notes with ALL of the following (Note: tests listed below must be repeated for confirmation of diagnosis):
      - Normal or elevated level of C1-INH antigenic protein (as defined by performing lab); AND
      - Low level (below the limits of the laboratory's normal reference range) C4 and C1-INH functional; AND
  - Documentation in medical chart of at least two attacks per month before treatment initiation; AND
  - Medication is not being used in combination with Cinryze; AND
  - Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
  - Dosage allowed: 60 units/kg of actual body weight twice weekly.
- For reauthorization
  - Member must be in compliance with all other initial criteria; AND
  - Chart notes have been provided that show the member's signs and symptoms of disease have improved and the number of acute attacks per month has decreased; AND
  - Log of medication use supported by medical chart or by claims data has been provided.

Clinical Implications/ Place in Therapy:

New drug for routine prophylaxis to prevent HAE attack was reviewed. Based on drug's clinical trials, package insert, and recommendations from professional society, it was determined that medication can be a viable option for our population. Preferred drug status is recommended.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Haegarda® (C1 esterase inhibitor [human]) subcutaneous injection
CSL Behring GmbH

INDICATION

Haegarda (C1 esterase inhibitor [human]) is a plasma-derived concentrate of C1 esterase inhibitor (C1INH) indicated for routine prophylaxis to prevent attacks of hereditary angioedema (HAE) in adolescent and adult patients (Haegarda prescribing information, 2017).

KEY POINTS

HAE is an uncommon autosomal dominant disorder that is characterized by a deficiency or dysfunction of the plasma C1INH protein (Benerji, 2015). Decreased C1INH activity results in recurrent episodes of swelling that most often affects the extremities, gastrointestinal tract, face, or larynx. The attacks are usually self-limiting; however, attacks in the abdomen may be associated with severe pain, nausea, and vomiting, while attacks in the larynx may result in fatal asphyxiation. C1INH is a critical regulator of the complement and kinin systems (Hemperly, 2013). It is thought that after activation of the complement, contact, and/or fibrinolytic systems following trauma, infection, or other unknown factors, low plasma levels of functional C1INH result in complete deregulation of the complement and contact systems, which eventually gives rise to increased bradykinin activation (Hereditary Angioedema Association [HAEA], 2017). Increased bradykinin levels in turn causes increased vascular permeability and edema.

HAE currently affects approximately 6,000 individuals to 10,000 individuals in the United States (US) (Food and Drug Administration [FDA], 2017). There are three types of HAE, which are classified based on the levels and activity of C1INH (Benerji, 2015). Type I HAE is the most prevalent form, accounting for approximately 80% to 85% of HAE cases, and it is characterized by a deficiency in plasma C1INH. Type II HAE is characterized by dysfunctional C1INH and accounts for approximately 15% of all HAE cases (Benerji, 2015; Hemperly, 2013). Type III HAE is currently referred to as HAE with normal C1INH and remains poorly understood, as patients have normal plasma levels of functional C1INH but continue to experience symptoms similar to types I and II HAE.

Haegarda (C1 esterase inhibitor [human]) is the first subcutaneous (SC) C1INH to prevent HAE attacks in adults and adolescents (FDA, 2017). Haegarda (C1 esterase inhibitor [human]) was approved on June 22, 2017 and received orphan drug designation.

CLINICAL EFFICACY

The efficacy and safety of Haegarda (C1 esterase inhibitor [human]) was evaluated in a prospective, randomized, double-blind, placebo-controlled, phase III crossover study in adults and pediatric patients ≥ 12 years of age with Types I or II HAE (Evidence level Ib; N = 90) (Longhurst, 2017). Prior to randomization, all patients entered a run-in period of up to eight weeks. Patients were then randomized in a 1:1:1:1 ratio to receive Haegarda (C1 esterase inhibitor [human]) 40 international units (IU)/kg SC twice weekly for the first 16 weeks followed by placebo SC twice weekly for an additional 16 weeks or, vice versa, or Haegarda (C1 esterase inhibitor [human]) 60 IU/kg SC twice weekly followed by placebo SC twice weekly, or vice versa. Patients were allowed to receive intravenous C1INH concentrate, Firazyr (icatibant), Kalbitor (ecallantide), or fresh-frozen plasma as rescue medications for on-demand treatment of attacks. Patients who had received intravenous C1INH prophylaxis within three months before screening were excluded. Overall, 82% to 91% of patients had type I HAE. The mean number of angioedema attacks per month during the run-in period was 4.6 in the 40 IU/kg treatment group and 4.0 in the 60 IU/kg treatment group. The primary endpoint was the number of attacks of angioedema. Secondary endpoints included percentage of patients reporting a response (≥ 50% reduction in the number of attacks versus placebo) and the number of times that rescue medications were utilized. Results of the study are described in Table 1.

Table 1: Efficacy of Haegarda (C1 esterase inhibitor [human]) in HAE Patients

Endpoint	Haegarda 40 IU/kg (n = 43)	Placebo (n = 44)	p-value	Haegarda 60 IU/kg* (n = 43)	Placebo (n = 42)	p-value
Mean Number of Attacks per Month (95% CI)	1.19 (0.54 to 1.85)	3.61 (2.96 to 4.26)	< 0.001	0.52 (0.00 to 1.04)	4.03 (3.51 to 4.55)	< 0.001
Mean % Reduction in Attacks Versus Placebo	55%	NA	NA	84%	NA	NA
Percentage of Patients Reporting ≥ 50% Reduction in Attacks Versus Placebo (95% CI)	76% (62% to 87%)	NA	NA	90% (77% to 96%)	NA	NA
Mean Number of Times Rescue Medication Used per Month (95% CI)	1.13 (-1.44 to 3.69)	5.55 (3.10 to 8.00)	0.02	0.32 (-0.33 to 0.97)	3.89 (3.23 to 4.55)	< 0.001

* Dose approved by Food and Drug Administration
CI = confidence interval
HAE = hereditary angioedema
IU = international units
NA = not available

(Longhurst, 2017)

Overall adverse events occurred in similar proportions of patients receiving Haegarda (C1 esterase inhibitor [human]) and placebo (Longhurst, 2017). The most common adverse events were mild and transient local injection site reactions. Overall, the study demonstrated that the prophylactic use of Haegarda (C1 esterase inhibitor [human]) SC twice weekly was well tolerated and significantly reduced the frequency of acute attacks in patients with HAE.

SAFETY

Warnings and precautions of Haegarda (C1 esterase inhibitor [human]) include severe hypersensitivity, risk of transmitting infectious agents (including the Creutzfeldt-Jakob disease agent), and thromboembolic events (Haegarda prescribing information, 2017). Haegarda (C1 esterase inhibitor [human]) is contraindicated in patients with hypersensitivity to any of its components. The most common adverse events that occurred in 4% or more of patients treated with Haegarda (C1 esterase inhibitor [human]) included injection site reaction (35% in the 60 IU/kg group vs. 24% in the placebo group), hypersensitivity (7% in the 60 IU/kg group vs. 1% in the placebo group), and nasopharyngitis (19% in the 60 IU/kg group vs. 7% in the placebo group).

PRODUCT AVAILABILITY

Haegarda (C1 esterase inhibitor [human]) is expected to launch in July of 2017 and will be available as a lyophilized powder supplied in single-use vials containing 2,000 or 3,000 IU of C1INH (RxPipeline, 2017; Haegarda prescribing information, 2017).

DOSAGE AND ADMINSTRATION

The recommended dosage for Haegarda (C1 esterase inhibitor [human]) is 60 IU/kg SC twice weekly every three or four days (Haegarda prescribing information, 2017).

PLACE IN THERAPY

- Berinert (C1 esterase inhibitor [human]), Kalbitor (ecallantide), Firazyr (icatibant), and Ruconest (C1 inhibitor [recombinant]) are FDA-approved for the treatment of HAE attacks (Prescribing information: Berinert, 2016; Firazyr, 2015; Kalbitor, 2014; Ruconest, 2015).
- Cinryze (C1 esterase inhibitor [human]) and Haegarda (C1 esterase inhibitor [human]) are FDA-approved for preventing HAE attacks (Cinryze prescribing information, 2016; Haegarda prescribing information, 2017). Cinryze (C1 esterase inhibitor [human]) is administered intravenously (IV), while Haegarda (C1 esterase inhibitor [human]) is administered via the SC route. Danocrine (danazol) is an oral androgen that is also indicated for preventing attacks of HAE (Danocrine prescribing information, 2016). However, it is associated with safety concerns including thromboembolism, benign intracranial hypertension, hepatic dysfunction, and fluid retention and should be avoided in pregnant or breastfeeding women, and in children (Danocrine prescribing information, 2016; Zuraw, 2013a).
- Indirect comparison shows Haegarda (C1 esterase inhibitor [human]) as potentially more effective than Cinryze (C1 esterase inhibitor [human]) (Longhurst, 2017; Zuraw, 2010). When compared with placebo, Haegarda (C1 esterase inhibitor [human]) 60 IU/kg reduced the rate of HAE attacks by roughly 84% while Cinryze (C1 esterase inhibitor [human]) reduced the rate of HAE attacks by approximately 51%.
- The US Hereditary Angioedema Association Medical Advisory Board (HAEA MAB) 2013 recommends the use of Cinryze (C1 esterase inhibitor [human]) or Danocrine (danazol) for short-term and long-term HAE prophylaxis (Zuraw, 2013a). Short-term prophylaxis is recommended prior to medical, surgical, and dental procedures to reduce the risk of an attack after physical stress or trauma. The use of long-term prophylaxis largely depends on patient specific conditions including attack frequency and severity, comorbid conditions, access to emergent treatment, and patient preference. Other agents for short- and long-term prophylaxis include oxandrolone, methyltestosterone, aminocaproic acid, and tranexamic acid; however, these agents lack an FDA indication for HAE management.
- The 2013 American Academy of Allergy, Asthma, and Immunology (AAAAI) practice parameters on HAE recommend fresh frozen plasma, C1INH replacement with Cinryze (C1 esterase inhibitor [human]), or short-term and high-dose anabolic androgen therapy with Danocrine (danazol) for short-term HAE prophylaxis (Zuraw, 2013b). For long-term HAE prophylaxis, C1INH replacement is the preferred choice of therapy. Other options for long-term prophylaxis include low to moderate doses of anabolic androgen therapy and antifibrinolytic therapy with tranexamic acid.
- Haegarda (C1 esterase inhibitor [human]) is not yet included in the AAAI or HAEA MAB treatment recommendations for HAE.

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CONDENSED DRUG MONOGRAPH PREPARED BY:

Elias Pittos, Pharm.D.
August 9, 2017

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

Pharmacy &Therapeutics Committee Summary Review
Idhifa® (enasidenib) – Celgene Corporation

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 3/8/2017

Therapeutic Class: Isocitrate dehydrogenase-2 inhibitor

FDA Approval Date: 8/1/2017

FDA Indication: Adult patients with relapsed or refractory acute myeloid leukemia with isocitrate dehydrogenase-2 mutation

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:
Idhifa is the first agent approved for the treatment of IDH2 mutation-positive relapsed or refractory AML. The 2017 NCCN Clinical Practice Guidelines in Oncology for AML recommend a cytarabine-containing chemotherapy regimen, hypomethylating agent +/- sorafenib, or enrollment in a clinical trial for patients with relapsed or refractory AML. Idhifa has currently not been evaluated for inclusion in the NCCN guidelines. Idhifa is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Idhifa® (enasidenib) tablets Celgene Corporation

INDICATION

Idhifa (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase (IDH)-2 mutation as detected by a Food and Drug Administration (FDA)-approved test (Idhifa prescribing information, 2017).

U.S. FDA-REVIEW DESIGNATION

Idhifa (enasidenib) was approved by the FDA on August 1, 2017 with a review designation of 1P (FDA, 2017a). Idhifa (enasidenib) is a new molecular entity that underwent priority review and was granted orphan drug designation (FDA, 2017b).

DRUG SUMMARY

Idhifa (enasidenib)	
Place in Therapy	• Idhifa is the first agent to be approved for the treatment of IDH2 mutation-positive relapsed or refractory AML. • The 2017 NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines)® for AML recommend a cytarabine-containing chemotherapy regimen, hypomethylating agent ± sorafenib, or enrollment in a clinical trial for patients with relapsed or refractory AML. • Idhifa has not been evaluated for inclusion in the NCCN Guidelines®.
Efficacy	• Approval for Idhifa was based on preliminary data from an ongoing, open-label, single-arm, multicenter, two-cohort phase I/II clinical trial that evaluated the efficacy and safety of Idhifa in patients with IDH2-mutation-positive relapsed or refractory AML. • Patients receiving Idhifa had a complete response rate of 19% and a median duration of response of 8.2 months. • The estimated completion date for the clinical trial is December 31, 2018.
Safety	• Boxed Warning: patients treated with Idhifa have experienced symptoms of differentiation syndrome, which can be fatal if left untreated. • Warnings/Precautions: differentiation syndrome, embryo-fetal toxicity. • Adverse Events (≥ 10%): nausea, diarrhea, vomiting, decreased appetite, differentiation syndrome, noninfectious leukocytosis, dysgeusia, increased total bilirubin, decreased calcium, decreased potassium, and decreased phosphorus.

AML = acute myeloid leukemia
IDH2 = isocitrate dehydrogenase-2
NCCN = National Comprehensive Cancer Network

CLINICAL PHARMACOLOGY

Mechanism of Action

Enasidenib inhibits the IDH2 enzyme mutations R140Q, R172S, and R172K (Idhifa prescribing information, 2017). Inhibition of mutant IDH2 leads to decreased 2-hydroxyglutarate (2-HG) levels, reduced blast counts, and increased percentages of mature myeloid cells.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Enasidenib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism*	Route of Elimination	$T_{1/2}$
Oral	57%	4 hours	55.8 L	98.5%	Multiple CYP enzymes† and UGTs‡	Feces: 89% Urine: 11%	137 hours

* Enasidenib is metabolized to AGI-16903, its N-dealkylated metabolite
† CYP enzymes involved in enasidenib metabolism include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
‡ UGTs involved in enasidenib metabolism include UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15
CYP = cytochrome P450 isoenzyme
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = elimination half-life
UGT = uridine diphosphate glucuronosyltransferase
(Idhifa prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for enasidenib.

CLINICAL EFFICACY

Idhifa (enasidenib) was approved based on preliminary data from an ongoing, open-label, single-arm, multicenter, two-cohort phase I/II clinical trial in patients with relapsed or refractory AML with an IDH2 mutation (N = 199) (Evidence level IIa) (ClinicalTrials.gov, 2017; FDA, 2017b; Idhifa prescribing information, 2017). Idhifa (enasidenib) was administered at a dose of 100 mg orally once daily (Idhifa prescribing information, 2017). The median follow-up was 6.6 months. Efficacy was based on the rate of complete response (CR), the rate of complete response with partial hematologic recovery (CRh), and the duration of response (DOR) for CR and CRh. Patients receiving Idhifa (enasidenib) had a CR of 19% (95% confidence interval [CI] 13 to 25) with a median DOR of 8.2 months (95% CI 4.7 to 19.4) and a CRh of 4% (95% CI 2 to 8) with a median DOR of 9.6 months (95% CI 0.7 to not available). The estimated completion date for the clinical trial is December 31, 2018 (ClinicalTrials.gov, 2017).

SAFETY

Boxed Warning

DIFFERENTIATION SYNDROME

Patients treated with Idhifa (enasidenib) can experience differentiation syndrome, which is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated (Idhifa prescribing information, 2017). Symptoms of differentiation syndrome include acute respiratory distress, requirement for supplemental oxygen, pulmonary infiltrates, pleural effusion, renal impairment, fever, and lymphadenopathy. Patients may also experience hepatic and multiorgan dysfunction. Differentiation syndrome has been observed with or without concomitant hyperleukocytosis, and as early as 10 days and up to five months after the start of Idhifa (enasidenib) therapy. If differentiation syndrome is suspected, corticosteroids and hemodynamic monitoring should be initiated until improvement.

Warnings and Precautions

Embryo-Fetal Toxicity

Idhifa (enasidenib) can cause embryo-fetal harm when administered to pregnant women (Idhifa prescribing information, 2017). Females of reproductive potential as well as males with female partners of reproductive potential should receive effective contraception during treatment with Idhifa (enasidenib) and for at least one month after the last dose.

Nursing Mothers

No data are available regarding the presence of enasidenib or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects on milk production (Idhifa prescribing information, 2017). Women are advised to not breastfeed during treatment with Idhifa (enasidenib) and for at least one month after the last dose.

Pediatric Use

Safety and efficacy of Idhifa (enasidenib) in pediatric patients have not been established (Idhifa prescribing information, 2017).

Geriatric Use

In the clinical trial, 61% of patients were 65 years of age and older, and 24% of patients were older than 75 years of age (Idhifa prescribing information, 2017). No overall differences in efficacy and safety were observed between older and younger patients.

Adverse Events

Table 2: Adverse Events Occurring in ≥ 10% of Patients Receiving Idhifa (enasidenib)

Adverse Event	Idhifa 100 mg daily (n = 214)
Nausea	50%
Diarrhea	43%
Vomiting	34%
Decreased appetite	34%
Differentiation syndrome	14%
Noninfectious leukocytosis	12%
Dysgeusia	12%
Increased total bilirubin	81%
Decreased calcium	74%
Decreased potassium	41%
Decreased phosphorus	27%

(Idhifa prescribing information, 2017)

PRODUCT AVAILABILITY

Idhifa (enasidenib) is available as a 50 mg or 100 mg tablet in bottles of 30 tablets (Idhifa prescribing information, 2017). Idhifa (enasidenib) launched on August 1, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

The recommended starting dose of Idhifa (enasidenib) is 100 mg orally once daily with or without food until disease progression or unacceptable toxicity (Idhifa prescribing information, 2017). For patients without disease progression or unacceptable toxicity, the minimum recommended treatment duration is six months. The dose of Idhifa (enasidenib) should be modified based on adverse events such as tumor lysis syndrome and increases in bilirubin, with details of dose modifications provided in the prescribing information.

APPROACHES TO TREATMENT

AML, which is characterized by the clonal expansion of myeloid blasts in the blood, bone marrow, and other tissues, is the most common form of adult acute leukemia in the United States (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2017). It is estimated that there will be 21,380 new cases and 10,590 deaths in 2017 (National Cancer Institute [NCI], 2017). AML occurs more commonly in older patients, with a median age of diagnosis of 68 years of age. In addition, AML is more common in men than women. The rate of new cases in men is 5.2 cases per 100,000 patients while the rate of new cases in women is 3.6 cases per 100,000 patients. While up to 70% of patients younger than 60 years of age and up to 50% of patients 60 years of age and older experience complete remission following induction chemotherapy, most patients develop disease recurrence within three years following diagnosis (Dohner, 2015; NCCN Guidelines®, 2017).

When patients present with AML, the signs and symptoms are generally non-specific and are manifestations of the pancytopenia which develops due to AML (American Cancer Society [ACS], 2016a). Patients may present with weight loss, night sweats, appetite loss, weakness, fatigue, infection, increased bruising and bleeding, and dyspnea upon exertion.

Patients are diagnosed with AML if they present with 20% or more of blasts in the bone marrow or peripheral blood (NCCN Guidelines®, 2017). Once diagnosed, AML is subcategorized based upon World Health Organization (WHO) classifications, which were last updated in 2016 (Arber, 2016). These subcategories include: AML with genetic abnormalities; AML with myelodysplasia-related changes; therapy-related myeloid neoplasms; AML, not otherwise specified; myeloid sarcoma; and myeloid proliferations related to Down syndrome.

Multiple prognostic factors have been identified which can be associated with favorable or unfavorable outcomes in AML (ACS, 2016b; NCCN Guidelines®, 2017). Different chromosome abnormalities and gene mutations can be positive or negative prognostic factors. Additional negative prognostic factors include age over 60 years, expression of cluster of differentiation (CD)-34 or p-glycoprotein on the surface of leukemia cells, high white blood cell count at the time of diagnosis, history of a prior blood disorder, treatment-related AML, active systemic infection at diagnosis, and the presence of leukemia cells in the central nervous system (ACS, 2016b).

Several different gene mutations have been identified in AML include nucleophosmin 1 (NPM1), FMS-like tyrosine kinase 3 (FLT3), CEBPA (CCAAT/enhancer binding protein alpha), IDH1, IDH2, deoxyribonucleic acid (cytosine-5)-methyltransferase 3A (DNMT3A), and KIT gene (NCCN Guidelines®, 2017). However, currently only FLT3 and IDH2 have FDA-approved targeted therapies (Prescribing information: Idhifa, 2017; Rydapt, 2017). FLT3, which is targeted by Rydapt (midostaurin), occurs in 10% to 30% of patients (NCCN Guidelines®, 2017). IDH2 mutations, which are exclusive of IDH1 mutations, occur in roughly 8% to 12% of patients with AML, with mutations specifically in R172 and R140 of the gene. The data regarding the impact of IDH2 mutation on outcomes have been inconsistent and its exact impact is unknown.

For patients with relapsed or refractory AML, the 2017 NCCN Guidelines® for AML recommend a cytarabine-containing chemotherapy regimen, a hypomethylating agent (i.e. 5-azacytidine or decitabine) ± sorafenib, or enrollment in a clinical trial (NCCN Guidelines®, 2017). Idhifa (enasidenib) has not yet been evaluated for guidance.

Of note, the FDA has recently approved Mylotarg (gemtuzumab ozogamicin) for the treatment of adults with newly diagnosed, CD33-positive AML as well as patients two years of age and older with relapsed or refractory CD33-positive AML (FDA, 2017c). CD33 expression in AML is extremely common, with documented presentation rates of 85% to 90% (Ehninger, 2014). IDH2 mutations and CD33 expression can occur concomitantly in AML and, therefore, Mylotarg (gemtuzumab ozogamicin) use may overlap with Idhifa (enasidenib) use (Patel, 2011). Mylotarg (gemtuzumab ozogamicin) has not yet been evaluated for guidance (NCCN Guidelines ®, 2017).

National Institute for Health and Care Excellence (NICE)

NICE currently only recognizes Vidaza (azacitidine) as a treatment option for AML (NICE, 2017). Vidaza (azacitidine) is recommended for the treatment of patients who have AML with 20% to 30% blasts and multilineage dysplasia, defined as the presence of ≥ 50% dysplastic cells in at least two cell lines by the WHO, and who are ineligible for hematopoietic stem cell transplantation (HSCT) (Arber, 2016; NICE, 2017). Vidaza (azacitidine) is not recommended for patients who are 65 years of age and older with more than 30% bone marrow blasts and who are ineligible for HSCT (NICE, 2017). Guidance for the use of Idhifa (enasidenib) in the setting of AML has not yet been reviewed by NICE.

PRODUCT COMPARISON

Mylotarg (gemtuzumab ozogamicin) is the only agent available that is a competitor for Idhifa (enasidenib). Neither Idhifa (enasidenib) nor Mylotarg (gemtuzumab ozogamicin) are not currently listed on the CVS Caremark National Formulary or any other drug list.

FORMULARY CONSIDERATIONS

Idhifa (enasidenib) is the first agent approved for the treatment of IDH2 mutation-positive, relapsed or refractory AML. Approval for Idhifa (enasidenib) was based on preliminary data from an ongoing, phase I/II clinical trial, which demonstrated an improvement in CR and CRh. The clinical trial has an estimated completion date for the primary endpoint is December 31, 2017 and an estimated study completion date of December 31, 2018. Idhifa (enasidenib) has a boxed warning for the development of differentiation syndrome, which can be fatal if left untreated. In addition, Idhifa (enasidenib) is associated with a high rate of adverse events, with the most common (i.e. ≥ 30%) being nausea, diarrhea, vomiting, decreased appetite, increased bilirubin, decreased calcium, and decreased potassium.

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DRUG MONOGRAPH PREPARED BY:

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September 22, 2017

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Pharmacy &Therapeutics Committee Summary Review
Kymriah® (tisagenlecleucel) – Novartis Pharmaceuticals

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2017

Therapeutic Class: CD19-directed genetically modified autologous T cell immunotherapy

FDA Approval Date: 8/30/2017

FDA Indication: B-cell precursor acute lymphoblastic leukemia (ALL)

Comparable Products: Yescarta (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred

- Member is 25 years of age or younger and has documentation of CD19 tumor expression; AND
- Member has B-cell acute lymphoblastic leukemia that is refractory or in second or later relapse as defined by one of the following:
  - 2nd or greater Bone Marrow (BM) relapse;
  - Any BM relapse after allogeneic stem cell transplantation (SCT) and must be > 6 months from SCT at the time of CAR-T cell immunotherapy infusion;
  - Refractory as defined by not achieving a complete remission (CR) after 2 cycles of a standard chemotherapy regimen chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapse leukemia;
  - Member with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia that is intolerant to or have failed 2 lines of tyrosine kinase inhibitor (TKI) therapy (e.g. imatinib mesylate (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna) or ponatinib (Iclusig)), or if TKI therapy is contraindicated;
  - Member is not eligible for allogeneic SCT; AND
- Member has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (leukapheresis); AND
- Healthcare facility/provider has enrolled in the Kymriah REMS and has training on the management of cytokine release syndrome (CRS) and neurological toxicities; AND
- Member must be premedicated with acetaminophen and an H1-antihistamine, and tocilizumab (Actemra) must be available in healthcare facility prior to infusion; AND
- Member has a life expectancy > 12 weeks; AND
- Member has not received prior CAR-T therapy.
- Dosage allowed: Weight 50 kg or less: administer 0.2 to 5.0 x 106CAR-positive viable T cells per kg body weight intravenously. Weight above 50

Clinical Implications/ Place in Therapy:
The first FDA approved CAR-T cell autologous immunotherapy was approved and reviewed for policy purposes. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. Healthcare facility or provider must be enrolled in the Kymriah REMS and has to have training on the management of cytokine release syndrome (CRS) and neurological toxicities.

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Kymriah

(tisagenlecleucel)

Novartis Pharmaceuticals Corporation

Kymriah

(tisagenlecleucel)

Click on the associated hyperlinks to view the source of information used.

Indication	**KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. (1)** **FDA Approval Date: Aug 30, 2017**
Pharmacology	Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy in which a patient's T cells are reprogrammed with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. CD3 zeta is a critical component for initiating T-cell activation and antitumor activity, while 4-1BB enhances expansion and persistence of tisagenlecleucel. After binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the tisagenlecleucel cells. Tisagenlecleucel is prepared from the patient's peripheral blood cells obtained via leukapheresis.
Dosage and Administration	**Strengths Available:** A single dose of KYMRIAH contains 0.2 to 5.0 x 106 CAR-positive viable T cells per kg of body weight for patients 50 kg and below or 0.1 to 2.5 x 108 CAR-positive viable T cells for patients above 50 kg, suspended in a single patient-specific infusion bag[see How Supplied/Storage and Handling (16)]. See the Certificate of Analysis (CoA) for actual cell count. The volume in the infusion bag ranges from 10 mL to 50 mL. **Dosage Frequency:** For autologous use only. For intravenous use only. • Verify the patient's identity prior to infusion. (2.2) • Premedicate with acetaminophen and an H1-antihistamine. (2.2) • Confirm availability of tocilizumab prior to infusion. (2.2,5.1) • Dosing is based on the number of chimeric antigen receptor (CAR) positive viable T cells. • For patients 50 kg or less, administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight intravenously. (2.1)

	• For patients above 50 kg, administer 0.1 to 2.5 x 108total CAR-positive viable T cells (non-weight based) intravenously. (2.1) ----------DOSAGE FORMS AND STRENGTHS---------- A single-dose unit contains 0.2 to 5.0 x 106 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 108 CAR-positive viable T cells for patients more than 50 kg, suspended in a patient-specific infusion bag. See the Certificate of Analysis (CoA) for actual cell count. (3)
Safety	The most common adverse reactions (incidence greater than 20%) are cytokine release syndrome, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium. (6) To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. **Contraindications:** None. (4)
Use in Specific Populations	8.1 Pregnancy Risk Summary There are no available data with KYMRIAH use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with KYMRIAH to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH administration should be discussed with the treating physician. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KYMRIAH in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIAH and any potential adverse effects on the breastfed infant from KYMRIAH or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with KYMRIAH.

Infertility

There are no data on the effect of KYMRIAH on fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIAH have been established in pediatric patients. Use of KYMRIAH is supported by a single-arm trial[see Clinical Studies (14)] that included 52 pediatric patients with relapsed or refractory B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients. Clinical studies of KYMRIAH for this indication did not include patients age 65 years and over.

Appendix: PI Highlights

For the complete Product Insert click here.

Product Description

KYMRIAH (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

KYMRIAH is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells, then transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to administration [see Dosage and Administration (2.5), How Supplied/Storage and Handling (16)]. The thawed product is a colorless to slightly yellow suspension of cells.

In addition to T cells, other cell populations, including monocytes, NK cells, and B cells, may be present. The formulation contains 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10 % Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv®dimethylsulfoxide (DMSO).

A single dose of KYMRIAH may contain up to 2.5 x 108CAR-positive viable T cells provided in a patient-specific infusion bag. Based on the patient's weight reported at the time of leukapheresis, one of two possible dose ranges will be prepared for the patient:

- For patients 50 kg or less: 0.2 to 5.0 x 106CAR-positive viable T cells per kg body weight
- For patients above 50 kg: 0.1 to 2.5 x 108CAR-positive viable T cells

The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis that is shipped with KYMRIAH. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

Indications and Usage

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Dosage and Administration

A single dose of KYMRIAH contains 0.2 to 5.0 x 106 CAR-positive viable T cells per kg of body weight for patients 50 kg and below or 0.1 to 2.5 x 108 CAR-positive viable T cells for patients above 50 kg, suspended in a single patient-specific infusion bag[see How Supplied/Storage and Handling (16)]. See the Certificate of Analysis (CoA) for actual cell count. The volume in the infusion bag ranges from 10 mL to 50 mL.

For autologous use only.

For intravenous use only.

2.1 Dose

- One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy followed by infusion of KYMRIAH [see Clinical Studies (14)].
- KYMRIAH is provided in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells* based on the patient weight reported at the time of leukapheresis. The dose is:
  – For patients 50 kg or less: administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight
  – For patients above 50 kg: administer 0.1 to 2.5 x 108 CAR-positive viable T cells

*See the Certificate of Analysis for the actual number of chimeric antigen receptor (CAR)-positive T cells in the product.

- Lymphodepleting chemotherapy: Fludarabine (30 mg/m2intravenous daily for 4 days) and cyclophosphamide (500 mg/m2intravenous daily for 2 days starting with the first dose of fludarabine). Infuse KYMRIAH 2 to 14 days after completion of the lymphodepleting chemotherapy.

2.2 Prepare for Infusion and Administration

Delay the infusion of KYMRIAH if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy [see Warnings and Precautions (5.1)].

Coordinate the timing of thaw of KYMRIAH and infusion. Once thawed, KYMRIAH may be stored at room temperature (20°C to 25°C) for up to 30 minutes. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIAH is available for infusion when the recipient is ready.

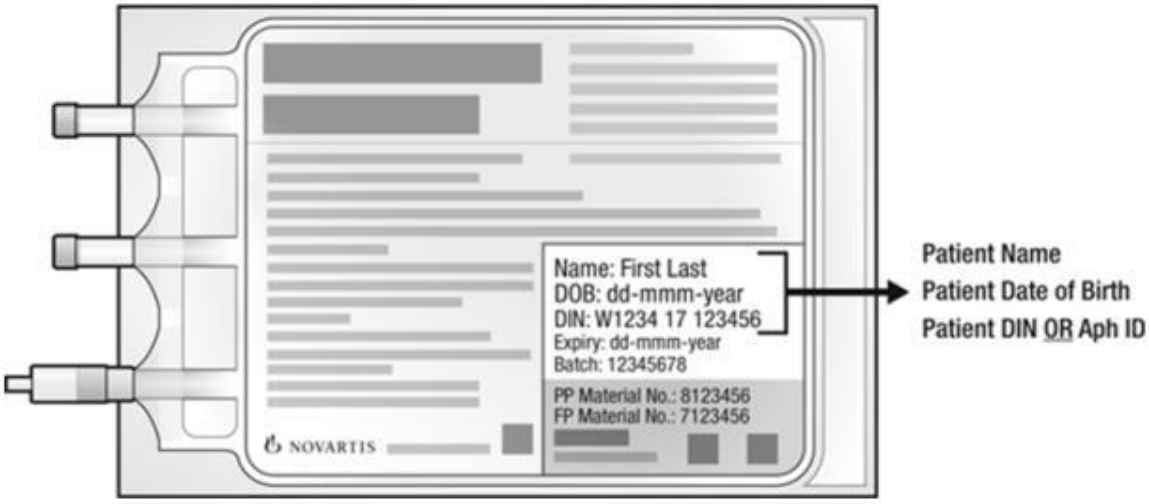
Preparation for Infusion

1. Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.

2. Premedicate patient with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to KYMRIAH infusion. Do not use corticosteroids at any time except in the case of a life-threatening emergency.

3. Confirm patient identity: Prior to KYMRIAH preparation, match the patient's identity with the patient identifiers on the KYMRIAH infusion bag. KYMRIAH is for autologous use only.

Note: The patient identifier number may be preceded by the letters DIN or Aph ID.



4. Inspect the infusion bag for any breaks or cracks prior to thawing. If the bag is compromised, do not infuse the contents. Call Novartis at 1-844-4KYMRIAH.

5. Place the infusion bag inside a second, sterile bag in case of a leak and to protect ports from contamination.

6. Thaw KYMRIAH at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Remove bag from thawing device immediately; do not store product bag at 37°C. Once KYMRIAH has been thawed and is at room temperature (20°C to 25°C), it should be infused within 30 minutes. Do not wash, spin down, and/or resuspend KYMRIAH in new media prior to infusion.

7. Inspect the contents of the thawed infusion bag for any visible cell clumps. If visible cell clumps remain, gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not infuse KYMRIAH if clumps are not dispersed, the infusion bag is damaged or leaking, or otherwise appears to be compromised. Call Novartis at 1-844-4KYMRIAH.

Administration

8. Confirm the patient’s identity with the patient identifiers on the infusion bag.

9. Administer KYMRIAH as an intravenous infusion at 10 mL to 20 mL per minute, adjusted as appropriate for smaller children and smaller volumes. The volume in the infusion bag ranges from 10 mL to 50 mL. Do NOT use a leukocyte-depleting filter.

– Prime the tubing prior to infusion with normal saline.
– Infuse all contents of the infusion bag.
– Rinse the infusion bag with 10 mL to 30 mL normal saline while maintaining a closed tubing system to assure as many cells as possible are infused into the patient.

KYMRIAH contains human cells genetically modified with a lentivirus. Follow local biosafety guidelines applicable for handling and disposal of such products. The product is prepared from autologous blood collected by leukapheresis. KYMRIAH may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation [see Warnings and Precautions (5.1)].Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1.

Table 1. Treatment of CRS

CRS Severity	Management
Prodromal Syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Overt CRS (one or more of the following): – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Severe or Life-Threatening CRS (one or more of the following): – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer tocilizumab – Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour – Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)
Resistant CRS: No clinical improvement in 12 to 18 hours, or worsening at any time, despite prior management.	Administer multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper

	quickly. If no response to steroids within 24 hours, repeat the administration of tocilizumab at – Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour – Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) If no response to the second dose of tocilizumab within 24 hours, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS.

Adverse Reactions

Most common adverse reactions (incidence greater than 20%) are hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, bleeding, hypotension, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium.

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Cytokine Release Syndrome[see Warnings and Precautions (5.1)]
- Neurological Toxicities[see Warnings and Precautions (5.2)]
- Infections and Febrile Neutropenia[see Warnings and Precautions (5.5)]
- Prolonged Cytopenias [see Warnings and Precautions (5.6)]
- Hypogammaglobulinemia[see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to KYMRIAH in the clinical trial (Study 1) in which 68 patients with pediatric and young adult relapsed/ refractory (R/R) B-cell ALL received CAR-positive viable T cells.

Based on a recommended dose which was weight-based, all patients received a single intravenous dose of KYMRIAH [see Clinical Studies (14)]. The most common adverse reactions were cytokine release syndrome (79%), hypogammaglobulinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%), tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (22%), acute kidney injury (22%), and delirium (21%).

Eleven deaths were reported for patients who received KYMRIAH, of which 2 deaths occurred within 30 days of infusion. Seven were disease-related, three were attributed to infections, and one to intracerebral hemorrhage. Of the two deaths before Day 30, one patient died with CRS and progressive leukemia and the second patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred.

The adverse reactions with greater or equal to 10% incidence for any Grade are summarized in Table 2.

Table 2. Selected Adverse Reactions (≥ 10%) Following Treatment with KYMRIAH (N=68)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Cardiac disorders		
aTachycardia	26	4
Gastrointestinal disorders		
Nausea	26	3
Diarrhea	26	1
Vomiting	26	1
Constipation	18	0
bAbdominal pain	16	3
General disorders and administration site conditions		
Pyrexia	40	15
Fatigue	22	0
Face edema	10	1
Edema peripheral	10	1
Chills	10	0
Immune system disorders		
Cytokine release syndrome	79	49
cHypogammaglobulinemia	43	7
Infections and infestations		
Infections-pathogen unspecified	41	16
Viral infectious disorders	26	18
Bacterial infectious disorders	19	13
Fungal infectious disorders	13	7
Investigations		
International normalized ratio increased	13	0

Metabolism and nutrition disorders		
Decreased appetite	37	15
Fluid overload	10	7
Musculoskeletal and connective tissue disorders		
Pain in extremity	16	1
Myalgia	15	0
Arthralgia	12	1
Back pain	10	3
Nervous system disorders		
dHeadache	37	3
eEncephalopathy	34	10
Psychiatric disorders		
fDelirium	21	4
Anxiety	13	3
Renal and urinary disorders		
gAcute kidney injury	22	13
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24	18
Cough	19	0
Pulmonary edema	16	10
Tachypnea	12	6
Pleural effusion	10	4
Nasal congestion	10	0
Vascular disorders		
Hypotension	31	22
Hypertension	19	6

aTachycardia includes tachycardia and sinus tachycardia.
bAbdominal pain includes abdominal pain, abdominal pain upper, gastrointestinal pain, abdominal pain lower.
cHypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, hypogammaglobulinemia.
dHeadache includes headache and migraine.

eEncephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, posterior reversible encephalopathy syndrome, somnolence, and automatism.
fDelirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.
gAcute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis.

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were:

Blood and lymphatic system disorders: disseminated intravascular coagulation (9%), histiocytosis lymphocytic hemophagocytosis (7%), coagulopathy (6%), Grade 3 and Grade 4 hypofibrinogenemia with Grade 3 and 4 CRS (16%)

Cardiac Disorders: cardiac arrest (4%), cardiac failure (7%)

Gastrointestinal disorders: abdominal compartment syndrome (1%)

General disorders and administration site conditions: multiple organ dysfunction syndrome (3%)

Immune system disorders: graft versus host disease (1%)

Investigations:blood creatinine increased (7%), activated partial thromboplastin time prolonged (6%)

Nervous System:intracranial hemorrhage (1%), seizure (3%)

Respiratory, thoracic, and mediastinal disorders: respiratory distress (6%), respiratory failure (6%), acute respiratory distress syndrome (4%)

Metabolism and nutrition disorders: tumor lysis syndrome (6%)

Vascular disorders: capillary leak syndrome (3%)

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 3.

Table 3. Selected Other Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Grade 3-4 Following Treatment with KYMRIAH based on CTCAEa (N=68)

	Grade 3 or 4 (%)
Increased Aspartate Aminotransferase	28
Hypokalemia	27
Increased Alanine Aminotransferase	21
Increased bilirubin	21
Hypophosphatemia	19

aCTCAE = Common Terminology Criteria for Adverse Events version 4.03

All patients experienced neutropenia, anemia and thrombocytopenia. See Table 4 for the incidences of Grade 3 and Grade 4 prolonged thrombocytopenia and prolonged neutropenia in responding patients.

Table 4. Prolonged Cytopenias Following Treatment with KYMRIAH

	N=52 (%)	
	Day 28	Day 56
Prolonged neutropeniaa	40	17
Prolonged thrombocytopeniaa	27	12
aGrade 3 and 4 observed within 14 days after Day 28 or Day 56 in responding patients		

6.2 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIAH was measured by determination of anti-murine CAR19 antibodies (anti-m CAR19) in serum pre- and post-administration. The majority of patients (86%) tested positive for pre-dose anti-m CAR19 antibodies in Study 1; however, the preexisting and treatment-induced antibodies were not associated with an impact on clinical response and did not have an impact on the initial expansion and persistence of KYMRIAH. Persistence of KYMRIAH was similar between patients with positive post-infusion anti-m CAR19 antibodies compared with patients with negative post-infusion anti-m CAR19 antibodies. There is no evidence that the presence of preexisting and treatment-induced anti-mCAR19 antibodies impact the safety or effectiveness of KYMRIAH.

Clinical Trials Results

Relapsed or Refractory (R/R) B-cell Acute Lymphoblastic Leukemia (ALL)

The efficacy of KYMRIAH in pediatric and young adults with R/R B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial (Study 1). In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects did not receive the product due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females of median age 12 years (range, 3-23 years). Seventy-three percent of patients were white, 10% were Asian, and 17% were of other races. Six (10%) had primary refractory disease, 30 (48%) had one prior stem cell transplantation, 5 patients (8%) had two stem cell transplantations. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m2daily for 4 days and cyclophosphamide 500 mg/m2 daily for 2 days) followed by a single dose of KYMRIAH. Of the 22 patients who had a WBC count < 1000/µL, 20 received lymphodepleting chemotherapy prior to KYMRIAH while 2 received KYMRIAH infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy.

The efficacy of KYMRIAH was established on the basis of complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) <

0.01% by flow cytometry (MRD-negative) (Table 6). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

Table 6 shows the efficacy results from this study.

Table 6. Efficacy Results in Pediatric and Young Adult Patients with R/R B-cell Precursor ALL

Results	N=63
CR/CRi1,2 95% CI	52 (83%) (71%, 91%) p<0.0001
CR3	40 (63%)
CRi4	12 (19%)
CR or CRi with MRD-negative bone marrow5,6 95% CI	52 (83%) (71%, 91%) p<0.0001
Duration of Remission7	N=52
Median (months)	Not reached
95% CI	(7.5, NE8)

Clinical Pharmacology

Mechanism of Action

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances the expansion and persistence of KYMRIAH. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the KYMRIAH cells.

Pharmacokinetics

Following infusion of KYMRIAH in pediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients, KYMRIAH exhibited an initial rapid expansion followed by a bi-exponential decline. KYMRIAH should be administered within 30 minutes of thawing at approximately 10-20 mL per minute.

A summary of pharmacokinetic parameters of KYMRIAH is provided in Table 5 below.

Table 5. Pharmacokinetic Parameters of KYMRIAH

Parameter	Summary Statistics	Responding Patients N=62	Non-Responding Patients N=8
Cmax (copies/mcg)	Geometric mean (CV%), n	34,700 (155.4), 61	20,000 (71.6%), 7
Tmax‡ (day)	Median [min;max], n	9.91 [0.008;27], 61	20.0 [0.03;62.7], 7
AUC0-28d (copies/mcg*day)	Geometric mean (CV%), n	318,000 (177.8), 61	156,000 (99.4), 6
T½ (day)	Geometric mean (CV%), n	16.8 (155.9), 54	2.52 (171.9), 3

‡A total of 7 patients had an early Tmax(< 0.03 days), the next lowest Tmax occurred at 5.7 days. Early Tmaxmay not be representative of the true maximal expansion, but rather representative of the amount of transgene present in the catheter from which sample was collected.

The Cmaxand AUC0-28d were approximately 2-fold higher in CR/CRi patients compared with non-responding (NR) patients.

KYMRIAH was present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that KYMRIAH distribution in bone marrow was 44% of that present in blood at Day 28 while at Months 3 and 6 KYMRIAH distributed at 67% and 69%, respectively, indicating high distribution to bone marrow.

Children < 10 years and between 10-18 years of age had 1.5 to 2-fold higher Cmaxand AUC0-28d than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the pharmacokinetics of KYMRIAH.

Some patients required tocilizumab and corticosteroids for the management of CRS. KYMRIAH continues to expand and persist following tocilizumab administration. Patients who have higher expansion are associated with higher CRS Grades[see Warnings and Precautions (5.1)]. Patients (n=18) treated with tocilizumab had 265% and 183% higher KYMRIAH AUC0-28d and Cmax, respectively, as compared to patients (n=44) who did not receive tocilizumab. Similarly, patients who received corticosteroids had 89% higher AUC0-28d compared with patients who did not receive corticosteroids.

Hepatic and renal impairment studies of KYMRIAH were not conducted.

Drug Interactions

HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false-positive results in patients who have received KYMRIAH.

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data with KYMRIAH use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with KYMRIAH to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH administration should be discussed with the treating physician. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KYMRIAH in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIAH and any potential adverse effects on the breastfed infant from KYMRIAH or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with KYMRIAH.

Infertility

There are no data on the effect of KYMRIAH on fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIAH have been established in pediatric patients. Use of KYMRIAH is supported by a single-arm trial[see Clinical Studies (14)] that included 52 pediatric patients with relapsed or refractory B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients. Clinical studies of KYMRIAH for this indication did not include patients age 65 years and over.

Pharmacy &Therapeutics Committee Summary Review

Mavyret® (glecaprevir and pibrentasvir) – AbbVie Inc

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2017

Therapeutic Class: NS3/4A protease inhibitor, NS5A inhibitor

FDA Approval Date: 8/3/2017

FDA Indication: Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection

Comparable Products: Zepatier, Technivie, Viekira, Olysio, Vosevi, Harvoni, Sovaldi, Epclusa

Proposed Designation & Rationale

Recommendation: Preferred

- For initial authorization for Hepatitis C (without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh Class A)):
  - Member must be 18 years of age or older; AND
  - Member has ONE of the following statuses:
    - Treatment-naïve with genotype 1, 2, 3, 4, 5 or 6 (laboratory documentation required); OR
    - Treatment-experienced with one of the following:
      - genotype 1, who previously have been treated with a regimen containing an HCV NS5A inhibitor1 or an NS3/4A protease inhibitor2, but not both; OR
      - genotype 1, 2, 3, 4, 5 or 6 with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor2 or NS5A inhibitor1 ; AND
  - Medication must be prescribed by a board certified hepatologist, gastroenterologist, infectious disease specialist or a nurse practitioner working with the above specialists; AND
  - Member's documented viral load taken within 6 months of beginning therapy and submitted with chart notes; AND
  - Member has documented current monthly negative urine drug and alcohol screens for 3 consecutive months (laboratory documentation required); AND
  - Member has evidence of liver fibrosis stage 2, 3 or 4 confirmed by liver biopsy, or elastography only (lab chart notes required) unless one of the following (fibrosis stage F0-4 covered):
    - Hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation);
    - Post liver transplantation;
    - Extrahepatic disease (i.e., kidney disease: proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis; cryoglobulinemia with end- organ manifestations (e.g., vasculitis));
    - HIV or HBV coinfection; AND
  - Member does not have any of the following:
    - Moderate to severe hepatic impairment (Child-Turcotte-Pugh B and C);
    - Currently on atazanavir and rifampin.
  - Dosage allowed: Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken orally once daily with food.

Clinical Implications/ Place in Therapy:

New drug for Hepatitis C without cirrhosis or with compensated cirrhosis was reviewed. Criteria for Mavyret was written based on package insert, clinical trials and guidelines from American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). Based on shorter treatment period and a broad genotype coverage it was recommended to place medication in preferred category of coverage.

References:

1. Mavyret [Package insert]. North Chicago, IL: AbbVie Inc.; August 2017.
2. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2017. Available at: https://www.hcvguidelines.org/.
3. Hepatitis C Information | Division of Viral Hepatitis | CDC. (2015, May 31). Retrieved from https://www.cdc.gov/hepatitis/hcv/index.htm.
4. Afdhal, N. (2012). Fibroscan (Transient Elastography) for the Measurement of Liver Fibrosis. Gastroenterology & Hepatology, 8(9), 605-607.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Mavyret™ (glecaprevir/pibrentasvir) tablets AbbVie Inc.

INDICATION

Mavyret (glecaprevir/pibrentasvir) is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype (GT) 1, 2, 3, 4, 5, or 6 infection (Mavyret prescribing information, 2017). Mavyret (glecaprevir/pibrentasvir) is also indicated for the treatment of adult patients with HCV GT1 infection who have been previously treated with a regimen containing an HCV nonstructural protein (NS) 5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Mavyret (glecaprevir/pibrentasvir) was approved by the FDA on August 3, 2017 with a review designation of 4P (FDA, 2017a). Mavyret (glecaprevir/pibrentasvir) is a fixed-dose combination (FDC) tablet of two new molecular entities that underwent priority review and was granted breakthrough therapy designation (FDA, 2017b). An agent may qualify for breakthrough therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2017c).

DRUG SUMMARY

	Mavyret (glecaprevir/pibrentasvir)
Place in Therapy	• Mavyret offers an additional treatment option as a pan-genotypic DAA for the treatment of patients with HCV infection with or without compensated cirrhosis and is the first FDA-approved treatment of eight weeks duration for all GT1 through 6 HCV infection in treatment naive patients without compensated cirrhosis. • Mavyret also offers an additional treatment option for the treatment of patients with HCV GT1 infection who were previously treated with an NS5A inhibitor and is the first FDA-approved agent for patients with HCV GT1 infections who have previously received treatment regimens containing an NS3/4A protease inhibitor. • Mavyret is the first pan-genotypic HCV treatment that is indicated in patients with CKD, including those on dialysis. • The AASLD/IDSA guidelines for the treatment of HCV recommend Mavyret as a pan-genotypic agent for treatment-naïve patients with or without compensated cirrhosis and for patients with GT1, 2, 4, 5, or 6 who are treatment experienced with or without compensated cirrhosis. The guidelines also recommend Epclusa (sofosbuvir/velpatasvir) as a pan-genotypic agent for patients with or without cirrhosis who are treatment naïve or experienced. For severe renal impairment (eGFR < 30 mL/min), the guidelines recommend Zepatier (elbasvir/grazoprevir) in patients with HCV GT 1a, 1b, and 4 and Mavyret in patients infected with HCV GT1 through 6.
Efficacy	• FDA approval for Mavyret was based on several phase II and phase III trials demonstrating high rates of SVR12 among patients with or without cirrhosis across HCV GT 1 through 6 who were treatment naïve or experienced. • The SURVEYOR and ENDURANCE trials exhibited SVR12 rates ranging from 90% to 100% in treatment naïve and PRS treatment experienced patients treated with eight to 12 weeks of Mavyret therapy across all GTs. • The EXPEDITION-4 trial showed SVR12 rates of nearly 100% in patients treated with Mavyret who had stage 4 or 5 CKD, including those on dialysis. • The MAGELLAN-1 trials demonstrated an SVR12 rate of 94% in patients treated with 16 weeks of Mavyret who had been previously treated with an NS5A inhibitor and an SVR12 rate of 100% in patients treated with 12 weeks of Mavyret who were experienced with an NS3/4A protease inhibitor.
Safety	• Warnings and precautions: risk of hepatitis B virus reactivation • Common AEs (≥ 10%): headache, fatigue

AASLD = American Association for the Study of Liver Disease
AE = adverse event
CKD = chronic kidney disease
DAA = direct-acting antiviral
eGFR = estimated glomerular filtration rate
FDA = Food and Drug Administration
GT = genotype
HCV = hepatitis C virus
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PRS = prior treatment with peginterferon, ribavirin, and/or sofosbuvir
RBV = ribavirin
SVR12 = sustained virologic response measured 12 weeks after treatment

CLINICAL PHARMACOLOGY

Mechanism of Action

Glecaprevir and pibrentasvir are direct-acting antiviral (DAA) agents that work against the HCV infection (Mavyret prescribing information, 2017). Glecaprevir is an inhibitor of the HCV NS3/4A protease, which is necessary for viral replication. Pibrentasvir is an inhibitor of HCV NS5A, which is required for viral ribonucleic acid (RNA) replication and virion assembly.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Glecaprevir/Pibrentasvir

Agent	Route of Administration	T_{max}	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
glecaprevir	Oral*	5 hours	97.5%	CYP3A4	Biliary excretion; 0.7% excreted in urine and 92.1% in feces	6 hours
pibrentasvir	Oral†	5 hours	> 99.9%	None	Biliary excretion; 0% excreted in urine and 96.6% in feces	13 hours

* Concurrent consumption of food may increase systemic exposure by 83% to 163%, relative to fasting
† Concurrent consumption of food may increase systemic exposure by 40% to 53%, relative to fasting
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{Max} = time to maximum plasma concentration

(Mavyret prescribing information, 2017)

Pharmacogenomics

Resistance

Clinical Studies with Treatment-naïve and Peginterferon, Ribavirin, and/or Sofosbuvir Treatment-experienced Patients with or without Cirrhosis

In a pooled analysis of patients naïve to NS3/4A PIs and NS5A inhibitors who received Mavyret (glecaprevir/pibrentasvir) for 8, 12, or 16 weeks, 22 patients (two with GT1, two with GT2, 18 with GT3 HCV infection) experienced virologic failure (Mavyret prescribing information, 2017). No subjects with HCV genotype 4, 5 or 6 infection experienced virologic failure. Of the two GT1 patients infected with HCV, one patient had treatment-emergent substitutions in NS3 and NS5A. The other patient had treatment-emergent in NS5A only. Among the two GT2-infected patients, no treatment-emergent substitutions were observed in NS3 or NS5A. Among the 18 GT3-infected patients, treatment-emergent NS3 substitutions were observed in 11 subjects. Treatment-emergent NS5A substitutions were observed in 16 subjects.

Clinical Studies in Patients with or without Cirrhosis Who Were Treatment Experienced to NS3/4A PIs and/or NS5A Inhibitors

Eleven HCV GT1 infected subjects (10 GT1a, one GT1b) with prior NS3/4A PI or NS5A inhibitor treatment experience who experienced virologic failure with Mavyret (glecaprevir/pibrentasvir) with or without ribavirin in the MAGELLAN-1 study were analyzed for treatment-emergent resistance (Mavyret prescribing information, 2017). Treatment-emergent NS3 substitutions were observed in 73% (8/11) of subjects. Nine of 10 subjects (90%, not including one subject missing NS5A data at failure) had treatment-emergent NS5A substitutions. All 11 subjects also had NS5A inhibitor resistance-associated substitutions detected at baseline, and 64% (7/11) had NS3 PI resistance-associated substitutions detected at baseline.

Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response

Patients who were treated with Mavyret (glecaprevir/pibrentasvir) and naïve to NS3/4A PIs and NS5A inhibitors were analyzed to determine the association between baseline amino acid polymorphisms and treatment outcome (Mavyret prescribing information, 2017). Baseline HCV polymorphisms in GT1, 2, 4, 5, and 6 did not have an impact on treatment outcome.

Among treatment-naïve, GT3-infected subjects without cirrhosis who received Mavyret (glecaprevir/pibrentasvir) for 8 weeks, an NS5A polymorphism was detected in 10% (18/181) of subjects, of whom 78% (14/18) achieved SVR12 (Mavyret prescribing information, 2017). Insufficient data are available to describe the impact of the NS5A polymorphism in GT3-infected patients with cirrhosis or prior treatment experience who received Mavyret (glecaprevir/pibrentasvir).

Cross-Resistance

There exists a possibility of cross-resistance between glecaprevir and other HCV NS3/4A PIs, and between pibrentasvir and other HCV NS5A inhibitors (Mavyret prescribing information, 2017). Cross-resistance is not expected between Mavyret (glecaprevir/pibrentasvir) and Sovaldi (sofosbuvir), peginterferon, or ribavirin. Among 23 NS3/4A PI-experienced/NS5A inhibitor-naïve patients who received Mavyret (glecaprevir/pibrentasvir) for 12 weeks in MAGELLAN-1 (excluding 2 non-virologic failure subjects), two subjects each had baseline NS3 resistance-associated substitutions. All 23 subjects achieved SVR12.

Among NS5A inhibitor-experienced/PI-naïve subjects who received Mavyret (glecaprevir/pibrentasvir) for 16 weeks, baseline NS5A resistance-associated substitutions were detected in 73% (11/15) of subjects with available data, of whom 91% (10/11) achieved SVR12 (Mavyret prescribing information, 2017). The non-SVR12 subjects who experienced on-treatment virologic failure had a genotype 1a infection with baseline NS5A resistance-associated substitutions.

CLINICAL EFFICACY

Table 2: Efficacy of Mavyret (glecaprevir/pibrentasvir) in the Treatment of HCV in Clinical Trials

Study and Study Design	N	Duration (weeks)	Population	Mavyret 300 mg/120 mg	Comparator	Primary Endpoint: SVR12 Rate		
Patients without Cirrhosis								
ENDURANCE-1 Zeuzem, 2016 (Randomized, open-label, phase III study; Evidence level Ib)	703	8 to 12	Patients with HCV GT1 without cirrhosis who were TN or TE with INF/PEG-IFN ± RBV, or Sovaldi (sofosbuvir) + RBV ± PEG-IFN	Mavyret FDC orally daily x 8 weeks	Mavyret FDC orally daily x 12 weeks	8 week regimen (n = 351)		99%
						12 week regimen (n = 352)		99.7%
SURVEYOR-1 & 2 (Part 2) Kwo, 2017 (Open-label, phase II study; Evidence level III)	175	8 to 12	Patients with HCV GT 1 through 6 without cirrhosis who were TN or TE with PEG-IFN + RBV	Mavyret FDC orally daily	NA	8 Week Therapy	TN or TE with GT1 (n = 34)	97%
							TN or TE with GT2 (n = 54)	98%
							TN with GT3 (n = 29)	97%
						12 Week Therapy	TE with GT3 (n = 24)	92%
							TN or TE with GT4, 5, or 6 (n = 34)	100%
SURVEYOR-2 (Part 4) Hassanein, 2016 (Open-label, phase II study; Evidence level III)	203	8	Patients with HCV GT2, 4, 5, or 6 without cirrhosis who were TN or TE with IFN/PEG-IFN ± RBV, or Sovaldi + RBV ± PEG-IFN	Mavyret FDC orally daily	NA	GT2 (n = 145)		98%
						GT4 (n = 46)		93%
						GT5 (n = 2)		90%
						GT6 (n = 10)		100%
ENDURANCE-3 Foster, 2017 (Randomized, open-label, active-controlled, phase III study; Evidence level Ib)	505	8 to 12	Patients with HCV GT3 without cirrhosis who were TN	Mavyret FDC orally daily	Sovaldi + Daklinza (daclatasvir) 60 mg daily	Mavyret x 8 weeks* (n = 157)		95%
						Mavyret x 12 weeks (n = 233)		95%
						Sovaldi + Daklinza 60 mg x 12 weeks (n = 115)		97%
ENDURANCE-4 Asselah, 2016 (Open-label, phase III study; Evidence level III)	121	12	Patients with HCV GT4, 5, or 6 without cirrhosis who were TN or TE with IFN/PEG-IFN ± RBV or Sovaldi + RBV ± PEG-IFN	Mavyret FDC orally daily	NA	GT4 (n = 76)		99%
						GT5 (n = 26)		100%
						GT6 (n = 19)		100%

* Non-randomized treatment arm
† 82% of patients were on hemodialysis
‡ Two patients discontinued treatment and were lost to follow up. When excluding these two patients in the modified ITT population, 100% of patients achieved SVR12
§ Six patients were treated with a decreased dose of Mavyret 200 mg/80 mg orally daily. Enrollment in this arm was halted early in the study to optimize dosing for further development. All 6 patients achieved SVR12.
‖ Prior DAA experience included boceprevir, telaprevir, ledipasvir/sofosbuvir, or simeprevir plus sofosbuvir
** The type of prior DAA experience (NS3/4A PI only, or NS5A inhibitor only, or both) was well balanced across treatment groups
†† There was one patient with HCV GT4 infection in the 12-week treatment group and 3 patients with HCV GT4 infection in the 16-week treatment group
‡‡ Previous NS3/4A PIs included asunaprevir, Victrelis (boceprevir), Incivek (telaprevir), Olysio (simeprevir), paritaprevir with ritonavir
§§ Previous NS5A inhibitors included Daklinza (daclatasvir), ledipasvir, and ombitasvir
CKD = chronic kidney disease
DAA = direct-acting antiviral
FDC = fixed-dose combination tablet
GT = genotype
HCV = hepatitis C virus
IFN = interferon
ITT = intention to treat
NA = not available
NS = nonstructural protein
PEG-IFN = peginterferon
PI = protease inhibitor
RBV = ribavirin
SVR12 = sustained virologic response at 12 weeks
TE = treatment experienced
TN = treatment naïve

(Asselah, 2016; Forns, 2017; Foster, 2017; Gane, 2016; Hassanein, 2017; Kwo, 2017; Mavyret prescribing information, 2017; Poordad, 2017a; Poordad, 2017b; Wyles, 2016; Zeuzem, 2016)

Table 2: Efficacy of Mavyret (glecaprevir/pibrentasvir) in the Treatment of HCV in Clinical Trials (continued)

Study and Study Design	N	Duration (weeks)	Population	Mavyret 300 mg/120 mg	Comparator	Primary Endpoint: SVR12 Rate		
Patients with Cirrhosis								
EXPEDITION-1 Forns, 2017 (Open-label, phase III study; Evidence level IIa)	146	12	Patients with HCV GT 1, 2, 4, 5, or 6 with compensated cirrhosis who were TN or TE with IFN/PEG-IFN ± RBV or Sovaldi + RBV ± PEG-IFN	Mavyret FDC orally daily	NA	GT1 (n = 90)		99%
						GT2 (n = 31)		100%
						GT4 (n = 16)		100%
						GT5 (n = 2)		100%
						GT6 (n = 7)		100%
SURVEYOR-2 (Part 3) Wyles, 2016 (Open-label, phase II study; Evidence level III)	131	12 to 16	Patients with HCV GT3 without cirrhosis or with compensated cirrhosis who were TN or TE with IFN/PEG-IFN ± RBV, or Sovaldi + RBV ± PEG-IFN	Mavyret FDC orally daily	NA	12 Week Therapy	TE without cirrhosis (n = 22)	91%
							TN with cirrhosis (n = 40)	98%
						16 Week Therapy	TE without cirrhosis (n = 22)	96%
							TE with cirrhosis (n = 47)	96%
Patients with CKD Stage 4 and 5								
EXPEDITION-4 Gane, 2016 (Open-label, phase II study; Evidence level IIa)	104	12	Patients with HCV GT 1 through 6 with stage 4 or 5 CKD† and with or without compensated cirrhosis who were TN or TE with IFN/PEG-IFN ± RBV or Sovaldi + RBV ± PEG-IFN	Mavyret FDC orally daily	NA	Overall‡		98%

* Non-randomized treatment arm
† 82% of patients were on hemodialysis
‡ Two patients discontinued treatment and were lost to follow up. When excluding these two patients in the modified ITT population, 100% of patients achieved SVR12
§ Six patients were treated with a decreased dose of Mavyret 200 mg/80 mg orally daily. Enrollment in this arm was halted early in the study to optimize dosing for further development. All 6 patients achieved SVR12.
‖ Prior DAA experience included boceprevir, telaprevir, ledipasvir/sofosbuvir, or simeprevir plus sofosbuvir
** The type of prior DAA experience (NS3/4A PI only, or NS5A inhibitor only, or both) was well balanced across treatment groups
†† There was one patient with HCV GT4 infection in the 12-week treatment group and 3 patients with HCV GT4 infection in the 16-week treatment group
‡‡ Previous NS3/4A PIs included asunaprevir, boceprevir, telaprevir, simeprevir, and paritaprevir with ritonavir
§§ Previous NS5A inhibitors included daclatasvir, ledipasvir, and ombitasvir

CKD = chronic kidney disease
DAA = direct-acting antiviral
FDC = fixed-dose combination tablet
GT = genotype
HCV = hepatitis C virus
IFN = interferon
ITT = intention to treat
NA = not available
NS = nonstructural protein
PEG-IFN = peginterferon
PI = protease inhibitor
RBV = ribavirin
SVR12 = sustained virologic response at 12 weeks
TE = treatment experienced
TN = treatment naïve

(Asselah, 2016; Forns, 2017; Foster, 2017; Gane, 2016; Hassanein, 2017; Kwo, 2017; Mavyret prescribing information, 2017; Poordad, 2017a; Poordad, 2017b; Wyles, 2016; Zeuzem, 2016)

Table 2: Efficacy of Mavyret (glecaprevir/pibrentasvir) in the Treatment of HCV in Clinical Trials (continued)

Study and Study Design	N	Duration (weeks)	Population	Mavyret 300 mg/120 mg	Comparator	Primary Endpoint: SVR12 Rate		
Patients with NS5A Inhibitor or PI Experience								
MAGELLAN-1 (Part 1) Poordad, 2017a (Randomized, open-label, phase II study; Evidence level Ib)	50§	12	Patients with HCV GT1 without cirrhosis and TE with DAA-based regimens‖ containing an NS3/4A PI, an NS5A inhibitor, or both**	Mavyret FDC orally daily + 800 mg of RBV daily	Mavyret FDC orally once daily	Mavyret + RBV (n = 22)		95%
						Mavyret (n = 22)		86%
MAGELLAN-1 (Part 2) Poordad, 2017b (Randomized, open-label, phase II study; Evidence level Ib)	91	12 to 16	Patients with HCV GT1 or GT4†† with or without cirrhosis and TE with DAA-based regimens containing an NS3/4A PI‡‡, an NS5A inhibitor§§, or both**	Mavyret FDC orally daily x 12 weeks	Mavyret FDC orally daily x 16 weeks	12 Week Therapy	TE with PI (n = 14)	100%
							TE with NS5A inhibitor (n = 16)	88%
							TE with PI + NS5A inhibitor (n = 14)	79%
						16 Week Therapy	TE with PI (n = 13)	100%
							TE with NS5A inhibitor (n = 18)	94%
							TE with PI + NS5A inhibitor (n = 16)	81%
Safety	The most common adverse events reported in studies included fatigue, headache, and nausea.							
Comments	Generalizability of study results may be limited by small numbers of participants with GT 4 through 6 may be too low to assess the efficacy of Mavyret in this patient population.							
Conclusion	Mavyret daily for 8, 12, or 16 weeks demonstrated high rates of SVR12 in TE or TN, compensated cirrhotic or non-cirrhotic patients across all HCV GTs with an acceptable safety profile.							

* Non-randomized treatment arm
† 82% of patients were on hemodialysis
‡ Two patients discontinued treatment and were lost to follow up. When excluding these two patients in the modified ITT population, 100% of patients achieved SVR12
§ Six patients were treated with a decreased dose of Mavyret 200 mg/80 mg orally daily. Enrollment in this arm was halted early in the study to optimize dosing for further development. All 6 patients achieved SVR12.
‖ Prior DAA experience included boceprevir, telaprevir, ledipasvir/sofosbuvir, or simeprevir plus sofosbuvir
** The type of prior DAA experience (NS3/4A PI only, or NS5A inhibitor only, or both) was well balanced across treatment groups
†† There was one patient with HCV GT4 infection who was treated for 12 weeks and 3 patients with HCV GT4 infection who were treated for 16 weeks
‡‡ Previous NS3/4A PIs included asunaprevir, boceprevir, telaprevir, simeprevir, and paritaprevir with ritonavir
§§ Previous NS5A inhibitors included daclatasvir, ledipasvir, and ombitasvir
CKD = chronic kidney disease
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TE = treatment experienced
TN = treatment naïve

(Asselah, 2016; Forns, 2017; Foster, 2017; Gane, 2016; Hassanein, 2017; Kwo, 2017; Mavyret prescribing information, 2017; Poordad, 2017a; Poordad, 2017b; Wyles, 2016; Zeuzem, 2016)

Efficacy and Safety Data in the Elderly

Fourteen percent of the total number of subjects in the phase II and phase III clinical trials for Mavyret (glecaprevir/pibrentasvir) were ≥ 65 years of age and 2% were ≥ 75 years of age (Mavyret prescribing information, 2017). Overall, no differences in safety or efficacy were observed between these subjects and younger subjects. There are no dose adjustments of Mavyret (glecaprevir/pibrentasvir) recommended in geriatric patients.

SAFETY

Contraindications

Mavyret (glecaprevir/pibrentasvir) is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (Mavyret prescribing information, 2017). Mavyret (glecaprevir/pibrentasvir) is also contraindicated with concomitant use of Reyataz (atazanavir) or Rifadin (rifampin).

Boxed Warning

RISK OF HEPATITIS B VIRUS (HBV) REACTIVATION IN PATIENTS CO-INFECTED WITH HCV AND HBV

HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV DAAs and were not receiving HBV antiviral therapy (Vosevi prescribing information, 2017). Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in hepatitis B surface antigen (HBsAg) positive patients and in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and hepatitis B core antibody [anti-HBc] positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV DAAs may be increased in these patients. Prior to initiating HCV treatment with Mavyret (glecaprevir/pibrentasvir), all patients should be tested for evidence of current or prior HBV infection by measuring HBsAg and ant-HBc. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatic flare or HBV reactivation during HCV treatment with Mavyret (glecaprevir/pibrentasvir) and during post-treatment follow-up.

Reproductive Risk

There are no adequate human data available to establish or determine whether or not Mavyret (glecaprevir/pibrentasvir) poses a risk to pregnancy outcomes (Mavyret prescribing information, 2017). Moreover, no evidence of adverse developmental outcomes was observed with the components of Mavyret (glecaprevir/pibrentasvir) administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of Mavyret (glecaprevir/pibrentasvir) in animal reproduction studies.

Nursing Mothers

It is not known whether the components of Mavyret (glecaprevir/pibrentasvir) are present in human breast milk, affect human milk production, or have effects on the breastfed infant (Mavyret prescribing information, 2017). Of note, when administered to lactating rodents, the components of Mavyret (glecaprevir/pibrentasvir) were present in the milk, without any effect on growth or development observed in the nursing pups. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Mavyret (glecaprevir/pibrentasvir) and any potential adverse effects on the breastfed child from Mavyret (glecaprevir/pibrentasvir) or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of Mavyret (glecaprevir/pibrentasvir) have not been established in pediatric patients < 18 years of age (Mavyret prescribing information, 2017).

Drug Interactions

Table 3: Potentially Significant Drug Interactions with Glecaprevir/Pibrentasvir

Interacting Agent	Outcome	Recommendation
digoxin	↑ digoxin exposure	↓ digoxin concentrations by ↓ dose by 50% or by modifying the dosing frequency and continue monitoring
dabigatran	↑ dabigatran	Refer to dabigatran prescribing information for dabigatran dose modifications in combination with P-gp inhibitors in the setting of renal impairment
carbamazepine	↓ glecaprevir, ↓ pibrentasvir	Coadministration is not recommended
rifampin	↓ glecaprevir, ↓ pibrentasvir	Coadministration with rifampin is contraindicated
ethinyl estradiol-containing drugs such as combined oral contraceptives	↔ glecaprevir, ↔ pibrentasvir	Coadministration is not recommended*
St. John's wort	↓ glecaprevir, ↓ pibrentasvir	Coadministration is not recommended
atazanavir	↑ glecaprevir, ↑ pibrentasvir	Coadministration with atazanavir is contraindicated
darunavir, lopinavir, ritonavir	↑ glecaprevir, ↑ pibrentasvir	Coadministration is not recommended
efavirenz	↓ glecaprevir, ↓ pibrentasvir	
atorvastatin, lovastatin, simvastatin	↑ atorvastatin, ↑ lovastatin, ↑ simvastatin	Coadministration is not recommended
pravastatin	↑ pravastatin	↓ pravastatin dose by 50% when coadministered with Mavyret due to risk of myopathy, including rhabdomyolysis
rosuvastatin	↑ rosuvastatin	Rosuvastatin may be administered with Mavyret at a dose ≤ 10 mg
fluvastatin, pitavastatin	↑ fluvastatin, ↑ pitavastatin	Lowest necessary statin dose based on risk/benefit assessment is recommended
cyclosporine	↑ glecaprevir, ↑ pibrentasvir	Coadministration of Mavyret is not recommended for use in patients requiring stable cyclosporine doses > 100 mg/day

* Coadministration may result in increased risk of ALT elevations
ALT = alanine aminotransferase
P-gp = P-glycoprotein

(Mavyret prescribing information, 2017)

Adverse Events

Data for adverse events of Mavyret (glecaprevir/pibrentasvir) in patients with or without compensated cirrhosis are derived from phase II and phase III clinical trials which evaluated approximately 2,300 patients infected with HCV GT1 through GT6 and received Mavyret (glecaprevir/pibrentasvir) for 8, 12, or 16 weeks (Mavyret prescribing information, 2017). The most common adverse events, in all grades, reported in ≥ 5% of patients receiving Mavyret (glecaprevir/pibrentasvir) treatment were headache (13%), fatigue (11%), and nausea (8%). In patients who experienced an adverse event, 80% reported an adverse event of mild severity.

PRODUCT AVAILABILITY

Mavyret (glecaprevir/pibrentasvir) is available in 4-week (monthly) and 8-week cartons (Mavyret prescribing information, 2017). Each weekly carton contains seven daily dose wallets. Each daily dose wallet contains three FDC tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir each. Mavyret (glecaprevir/pibrentasvir) launched on August 7, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

The recommended dose of Mavyret (glecaprevir/pibrentasvir) is three tablets administered orally once daily with food (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) (Mavyret prescribing information, 2017). No dosage adjustment is recommended in patients with renal impairment, including those on dialysis. Mavyret (glecaprevir/pibrentasvir) is not recommended in moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposure of glecaprevir and pibrentasvir in these patients. Table 5 provides the recommended treatment regimen and duration based on patient genotype, treatment history, and cirrhosis status.

Table 4: Recommended Treatment Regimen and Duration for Mavyret (glecaprevir/pibrentasvir) in TN or TE Adult Patients with or without Compensated Cirrhosis (Child-Pugh A)

Genotype	Previous HCV Treatment Regimen	Treatment Duration	
		No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	TN	8 weeks	12 weeks
1	An NS5A inhibitor* without prior treatment with an NS3/4A PI	16 weeks	16 weeks
	An NS3/4A PI† without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS	8 weeks	12 weeks
3	PRS	16 weeks	16 weeks

* In clinical trials, patients were treated with prior regimens containing Harvoni (ledipasvir/sofosbuvir) or Daklinza (daclatasvir) with peginterferon and ribavirin

† In clinical trials, patients were treated with prior regimens containing Olysio (simeprevir) and Sovaldi (sofosbuvir), or Olysio, Victrelis (boceprevir), or Incivek (telaprevir) with peginterferon and ribavirin

HCV = hepatitis C virus

NS = nonstructural protein

PI = protease inhibitor

PRS = prior treatment with regimens containing interferon, peginterferon, ribavirin, and/or Sovaldi (sofosbuvir), but no prior treatment experience with an NS3/4A PI or NS5A inhibitor

TE = treatment experienced

TN = treatment naive

(Mavyret prescribing information, 2017)

APPROACHES TO TREATMENT

Approximately 2.7 to 3.9 million individuals in the United States and 71 million people worldwide are infected with chronic HCV (Centers for Disease Control and Prevention [CDC], 2017; World Health Organization [WHO], 2017). HCV transmission occurs primarily through exposure to infected blood. This exposure exists in the context of injection drug use, blood transfusions and solid organ transplantations from infected donors before 1992, recipients of clotting factor concentrates before 1987, chronic hemodialysis, needlestick injuries in healthcare settings, or infants born to an infected mother (CDC, 2017). HCV can also be spread, although less frequently, through sexual intercourse with an infected person, sharing contaminated personal items with infectious blood (e.g., razors or toothbrushes), or other invasive procedures performed in a healthcare setting (e.g., injections). Transmission from blood products and organ transplants was virtually eliminated by the introduction of blood screening in 1992. The risk of transmitting HCV through blood products has been largely decreased due to more advanced screening tests utilized in blood banks. Individuals born between 1945 and 1965 account for almost three-fourths of HCV infections in the United States (American Association for the Study of Liver Diseases [AASLD] and Infectious Diseases Society of America [IDSA] Guidelines, 2017).

HCV is a small, enveloped RNA virus that has been allocated to a unique genus *Hepacivirus* within the family *Flaviridae* (Thomson, 2005). HCV replicates in the cytosol of infected hepatocytes (Soriano, 2005). Similar to other RNA-dependent polymerases, the HCV RNA polymerase (NS5B) generates considerable genetic diversity. On the basis of variations in the nucleotide sequence of HCV, six genotypes (numbered 1 to 6) and more than 50 subtypes (e.g., 1a and 1b) have been identified (CDC, 2017; Khuroo, 2004). HCV genotypes and subtypes are intrinsic characteristics of the transmitted viral strain and do not change during the course of the infection. In the United States, the prevalence of HCV is 1.3% of the general population (Petruzziello, 2016). Approximately 75.2% of patients are infected with HCV GT1, 12.5% with GT2, 10.4% with GT3, and less than 2% with GT4, GT5, or GT6 (Messina, 2014).

The natural history of HCV is quite variable (Wong, 2005). After exposure, 75% to 85% of patients become chronically infected, which is an infection that persists for at least six months (CDC, 2017). HCV is also associated with slowly progressive hepatic fibrosis, with 60% to 70% of patients developing chronic liver disease, 5% to 20% developing cirrhosis over 20 years to 30 years, and 1% to 5% dying from hepatocellular carcinoma (HCC) or cirrhosis. Table 5 illustrates factors that can be associated with a higher risk of fibrosis progression with HCV (AASLD/IDSA, 2017). Approximately 15% to 25% of patients spontaneously clear the infection and do not develop chronic infection (CDC, 2017). The age of infection is linked with risk for chronicity and rate of disease progression, with children and young adults more likely to have spontaneous clearance of the infection and less likely to develop cirrhosis compared with older individuals (Wong, 2005). Although 80% of acute HCV cases are asymptomatic, the most common symptoms include jaundice, fatigue, dark urine, clay-colored stool, abdominal pain, loss of appetite, and nausea (CDC, 2017; WHO, 2017). Most patients who develop chronic HCV will not exhibit any symptoms until liver complications have developed (CDC, 2017).

Table 5: Factors Associated With a Higher Risk of Fibrosis Progression with HCV

Host: Non-Modifiable	Host: Modifiable	Viral
• Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant	• Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance	• Genotype 3 • Coinfection with HBV or HIV

HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus

(AASLD/IDSA, 2017)

In the last few years, treatment for HCV has changed dramatically (Pawlotsky, 2014). The approval of several oral DAAs, including combination products, has revolutionized treatment for HCV. Interferon (IFN)-containing-regimens have largely been replaced by all oral, IFN-free, and ribavirin-free therapies. These newer IFN-free regimens are well tolerated with shorter treatment durations and have cured more than 90% of patients in clinical trials compared with older IFN-based regimens with cure rates between 40% and 45% (Bourliere, 2017; Lam, 2015).

First generation DAAs, Incivek (telaprevir) and Victrelis (boceprevir), were introduced in 2011 and were PIs administered with peginterferon and Rebetol (ribavirin) with estimated SVR rates of 70% (Lam, 2015). Between 2013 and 2015, the next generation of DAAs were introduced and focused on inhibiting one of three NSs involved in the replication of the HCV and include an NS3/4A PI (Olysio [simeprevir]), an NS5A inhibitor (Daklinza [daclatasvir]), an NS5B inhibitor (Sovaldi [sofosbuvir]), and combination regimens (Harvoni [ledipasvir/sofosbuvir], Technivie [ombitasvir/paritaprevir/ritonavir], and Viekira Pak [ombitasvir/paritaprevir/ritonavir and dasabuvir]).This generation of DAAs is effective across several HCV genotypes, with Harvoni (ledipasvir/sofosbuvir) as the first agent as a single tablet complete regimen. Epclusa (sofosbuvir/velpatasvir) was approved in 2016 and was the first pan-genotypic agent to provide an oral treatment regimen without the co-administration of ribavirin or an IFN agent for the treatment of patients with HCV with and without cirrhosis (FDA, 2016). Vosevi (sofosbuvir/velpatasvir/voxilaprevir) was approved on July 18, 2017 and is the first treatment approved for patients infected with HCV GT1 through 6 and who have been previously treated with an NS5A inhibitor (FDA, 2017d). Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is also the first FDA-approved treatment for patients with HCV GT1a and 3 who previously failed treatment with Sovaldi (sofosbuvir). The introduction of these agents to the HCV treatment landscape has resulted in IFN- and ribavirin-free treatment regimens that are well tolerated, safe, and have demonstrated very high SVR rates.

The goal of treatment is to reduce all-cause mortality and prevent complications of HCV infection (e.g., end-stage liver disease and HCC); this is principally achieved by eradication of infection through achievement of SVR (AASLD/IDSA, 2017). Improvement in liver histology, including improvement in fibrosis, has been observed in those with SVR. SVR may also be associated with an improvement in health-related quality of life (Spiegel, 2005). The joint 2017 AASLD/IDSA guidelines state that all patients with HCV should be treated, except for those with a short life expectancy (< 12 months) who cannot be cured with HCV treatment, liver transplantation, or other directed therapy (AASLD/IDSA, 2017). Table 6 summarizes the AASLD/IDSA 2017 guideline recommendations for the treatment of HCV GT1 through 6 in treatment-naïve and treatment-experienced patients. A summary of agents recommended for patients with decompensated cirrhosis is not discussed as Mavyret is contraindicated in the setting of severe hepatic impairment.

Mavyret (glecaprevir/pibrentasvir) was approved on August 3, 2017 and is another pan-genotypic DAA indicated for patients infected with HCV with or without compensated cirrhosis, including patients with severe kidney disease and those on dialysis (FDA, 2017b). Mavyret (glecaprevir/pibrentasvir) is also indicated in patients with GT1 who have been previously treated with a regimen either containing an NS5A inhibitor or an NS3/4A PI but not both.

Table 6: AASLD/IDSA 2017 Recommended Agents for HCV GT 1a, 1b, 2, 3, 4, 5 and 6*

HCV Genotype	Medications	Length of Therapy
Treatment-Naïve Patients		
1a/1b	*No Cirrhosis*	12 weeks
	Zepatier (elbasvir/grazoprevir)†	
	Harvoni (ledipasvir/sofosbuvir)‡	
	Mavyret (glecaprevir/pibrentasvir)	8 weeks
	Epclusa (sofosbuvir/velpatasvir)	12 weeks
2	**Epclusa**	
	Mavyret	8 weeks
3	**Epclusa**	12 weeks
	Mavyret	8 weeks
1a/1b	*Compensated Cirrhosis*	12 weeks
	Zepatier†	
	Harvoni	
	Epclusa	
	Mavyret	
2	**Epclusa**	
	Mavyret	
3	**Epclusa**§	
	Mavyret	
4	*With and Without Cirrhosis*	8 weeks (no cirrhosis)/ 12 weeks (cirrhosis)
	Mavyret (I, B)	
	Epclusa	12 weeks
	Zepatier (IIa, B)	
	Harvoni (IIa, B)	
5, 6	**Epclusa** (I, B)	
	Harvoni (IIa, B)	
	Mavyret	8 weeks (no cirrhosis)/ 12 weeks (cirrhosis)

* Unless otherwise noted, all recommendations depicted are class I, level A (evidence and/or general agreement that a given treatment is beneficial, useful, and effective and data are derived from multiple randomized clinical trials, meta-analyses, or equivalent).
† Patients in whom no baseline NS5A RAVs for elbasvir are detected for HCV-GT1a
‡ Treatment duration may be 8 weeks in patients who are non-black, HIV-uninfected, and whose HCV RNA level is < 6 million IU/mL
§ Resistance-associated variants testing for Y93H is recommended for cirrhotic patients and RBV should be included in regimen if present
‖ For patients with prior NS5A inhibitor failure and cirrhosis, the addition of RBV is recommended (IIa, C)

AASLD = American Association for the Study of Liver Diseases
eGFR = estimated glomerular filtration rate
ESRD = end stage renal disease
GT = genotype
HCV = hepatitis C virus
IU = international units
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PI = protease inhibitor
RAV = resistance-associated variant
RBV = ribavirin
RNA = ribonucleic acid

(AASLD/IDSA, 2017)

Table 6: AASLD/IDSA 2017 Recommended Agents for HCV GT 1a, 1b, 2, 3, 4, 5 and 6* (continued)

HCV Genotype	Medications	Length of Therapy
Treatment-Naïve and Treatment-Experienced Patients		
1, 4, 5, 6	*Post Liver Transplantation without Cirrhosis*	12 weeks
	Mavyret	
	Harvoni + RBV	
2, 3	**Mavyret**	
	Daklinza (daclatasvir) **+ Sovaldi** (sofosbuvir) **+** low initial dose of RBV (II, A)	
1, 4, 5, 6	*Post Liver Transplantation with Compensated Cirrhosis*	
	Harvoni + RBV	
2, 3	**Daklinza + Sovaldi+** low initial dose of RBV (II, A)	
1a, 1b, 4	Severe Renal Impairment (eGFR < 30 mL/min) or ESRD	12 weeks
	Zepatier (I, B)	
1, 2, 3, 4, 5, 6	**Mavyret** (I, B)	8 to 16 weeks

* Unless otherwise noted, all recommendations depicted are class I, level A (evidence and/or general agreement that a given treatment is beneficial, useful, and effective and data are derived from multiple randomized clinical trials, meta-analyses, or equivalent).
† Patients in whom no baseline NS5A RAVs for elbasvir are detected for HCV-GT1a
‡ Treatment duration may be 8 weeks in patients who are non-black, HIV-uninfected, and whose HCV RNA level is < 6 million IU/mL
§ Resistance-associated variants testing for Y93H is recommended for cirrhotic patients and RBV should be included in regimen if present
‖ For patients with prior NS5A inhibitor failure and cirrhosis, the addition of RBV is recommended (IIa, C)
AASLD = American Association for the Study of Liver Diseases
eGFR = estimated glomerular filtration rate
ESRD = end stage renal disease
GT = genotype
HCV = hepatitis C virus
IU = international units
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PI = protease inhibitor
RAV = resistance-associated variants
RBV = ribavirin
RNA = ribonucleic acid

(AASLD/IDSA, 2017)

Table 6: AASLD/IDSA Recommended Agents for HCV GT 1a, 1b, 2, 3, 4, 5, and 6* (continued)

HCV Genotype	Medications	Length of Therapy
Patients in whom Previous Treatment with PEG/RBV has Failed		
1a/1b	*No Cirrhosis*	12 weeks
	Zepatier†	
	Harvoni	
	Mavyret	8 weeks
	Epclusa	12 weeks
2	**Epclusa**	
	Mavyret	8 weeks
3	**Epclusa**§	12 weeks
4	**Epclusa**	12 weeks
	Mavyret (I, B)	8 weeks
	Zepatier (IIa, B)	12 weeks
	Harvoni (IIa, B)	
1a/1b	*Compensated Cirrhosis*	
	Zepatier†	
	Mavyret (I, B)	
	Epclusa	
2	**Epclusa**	
	Mavyret (I, B)	
3	**Zepatier + Sovaldi** (I, B)	
	Vosevi (sofosbuvir/velpatasvir/voxilaprevir) (IIb, B)	
4	**Epclusa** (I, A)	
	Zepatier (IIa, B)	
	Mavyret (IIa, B)	
5, 6	*With and Without Cirrhosis*	8 weeks (no cirrhosis)/ 12 weeks (cirrhosis)
	Mavyret (IIa, B)	
	Harvoni (IIa, B)	12 weeks
	Epclusa (IIa, B)	

* Unless otherwise noted, all recommendations depicted are class I, level A (evidence and/or general agreement that a given treatment is beneficial, useful, and effective and data are derived from multiple randomized clinical trials, meta-analyses, or equivalent).
† Patients in whom no baseline NS5A RAVs for elbasvir are detected for HCV-GT1a
‡ Treatment duration may be 8 weeks in patients who are non-black, HIV-uninfected, and whose HCV RNA level is < 6 million IU/mL
§ Resistance-associated variants testing for Y93H is recommended for cirrhotic patients and RBV should be included in regimen if present
‖ For patients with prior NS5A inhibitor failure and cirrhosis, the addition of RBV is recommended (IIa, C)

AASLD = American Association for the Study of Liver Diseases
eGFR = estimated glomerular filtration rate
ESRD = end stage renal disease
GT = genotype
HCV = hepatitis C virus
IU = international units
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PI = protease inhibitor
RAV = resistance-associated variants
RBV = ribavirin
RNA = ribonucleic acid

(AASLD/IDSA, 2017)

Table 6: AASLD/IDSA Recommended Agents for HCV GT 1a, 1b, 2, 3, 4, 5, and 6* (continued)

HCV Genotype	Medications	Length of Therapy
Patients in whom Previous Treatment with NS3 PI + PEG/RBV without Cirrhosis		
1	*No Cirrhosis:*	12 weeks
	Harvoni	
	Epclusa	
	Mavyret (IIa, B)	
	Compensated Cirrhosis:	
	Epclusa	
	Mavyret (IIa, B)	
Patients in whom Previous Treatment with Sofosbuvir-Containing Regimen Failed		
1	*No Cirrhosis:*	12 weeks
	Mavyret (IIa, B)	
1a	**Vosevi**	
1b	**Epclusa** (IIa, B)	
1	*Compensated Cirrhosis:*	
	Mavyret (IIa, B)	
1a	**Vosevi**	
1b	**Epclusa** (IIa, B)	
2	*With and Without Cirrhosis*	
	Epclusa (I, B)	
	Mavyret (IIb, B)	
NS5A Inhibitor DAA-Experienced Patients		
1, 4	*With and Without Cirrhosis*	12 weeks
	Vosevi	
3	**Vosevi**‖	
5, 6	**Vosevi**‖ (IIa, B)	

* Unless otherwise noted, all recommendations depicted are class I, level A (evidence and/or general agreement that a given treatment is beneficial, useful, and effective and data are derived from multiple randomized clinical trials, meta-analyses, or equivalent).
† Patients in whom no baseline NS5A RAVs for elbasvir are detected for HCV-GT1a
‡ Treatment duration may be 8 weeks in patients who are non-black, HIV-uninfected, and whose HCV RNA level is < 6 million IU/mL
§ Resistance-associated variants testing for Y93H is recommended for cirrhotic patients and RBV should be included in regimen if present
‖ For patients with prior NS5A inhibitor failure and cirrhosis, the addition of RBV is recommended (IIa, C)
AASLD = American Association for the Study of Liver Diseases
eGFR = estimated glomerular filtration rate
ESRD = end stage renal disease
GT = genotype
HCV = hepatitis C virus
IU = international units
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PI = protease inhibitor
RAV = resistance-associated variants
RBV = ribavirin
RNA = ribonucleic acid

(AASLD/IDSA, 2017)

National Institute for Health and Care Excellence (NICE)

Guidance regarding Mavyret (glecaprevir/pibrentasvir) is scheduled to be released in March 2018, and guidance regarding the treatment of hepatitis C virus is currently in progress without an anticipated publication date (NICE, 2017; NICE, 2016).

Table 7: Comparison of Select FDA-Approved Agents for the Treatment of HCV GT1 through 6

Agent	Advantages	Disadvantages
All Agents	• All agents have comparable efficacy across GTs and have demonstrated high SVR rates • Allow for IFN-free treatment regimens • All agents are included in the AASLD/IDSA guidelines for HCV and recommendations are similar to the FDA-approved indications	• HBV reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death • Many potential drug interactions
Daklinza (daclatasvir)	• FDA-approved for HCV GT1 or 3 in compensated or decompensated cirrhosis • Recommended treatment regimen for multiple patient populations (e.g., TN or TE, HCV/HIV co-infection, or post-liver transplant) • Recommended by AASLD/IDSA guidelines for use in GT2 or 3 in TN or TE patients with or without cirrhosis or post-liver transplant	• When coadministered with sofosbuvir and amiodarone, serious symptomatic bradycardia may occur
Epclusa (sofosbuvir/velpatasvir)	• Pan-genotypic DAA in compensated or decompensated cirrhosis • One tablet daily with or without food • No dose adjustment required for hepatic impairment • Recommended treatment regimen for multiple patient populations (e.g., TN, TE, HIV/HCV co-infection).	• Use with acid reducing agents may decrease the concentration of velpatasvir • Coadministration with amiodarone may result in serious, symptomatic bradycardia
Harvoni (ledipasvir/ sofosbuvir)	• FDA-approved for HCV GT1, 4, 5, or 6 and in compensated or decompensated cirrhosis • Recommended treatment regimen for multiple patient populations (e.g. TN, TE, HCV/HIV coinfection, post-liver transplant) • Treatment duration may be decreased to 8 weeks in TN GT1 patients without cirrhosis	• Use with acid reducing agents may decrease the concentration of ledipasvir • Coadministration with amiodarone may result in serious, symptomatic bradycardia
Mavyret (glecaprevir/ pibrentasvir)	• Pan-genotypic DAA in patients with or without cirrhosis and in patients with HCV/HIV co-infection or CKD with hemodialysis • Offers 8 week therapy option for TN patients without cirrhosis across all genotypes and for TE patients without cirrhosis with GT1, 2, 4, 5, 6 • FDA-approved for patients with GT1 experienced with an NS5A inhibitor or NS3/4A PI	• Three tablets daily with food • Contraindicated in patients with severe hepatic impairment (Child-Pugh C)

AASLD = American Association for the Study of Liver Diseases
CKD = chronic kidney disease
CYP = cytochrome P450 isoenzyme system
DAA = direct-acting antiviral
ER = extended release
FDA = Food and Drug Administration
GT = genotype
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus
IDSA = Infectious Diseases Society of America
IFN = interferon-alfa
NS = nonstructural protein
OATP = organic anion transporting polypeptides
P-gp = P-glycoprotein
PEG IFN = peginterferon
PI = protease inhibitor
RBV = ribavirin
TE = treatment-experienced
TN = treatment-naive

Table 7: Comparison of Select FDA-Approved Agents for the Treatment of HCV GT1 through GT6 (continued)

Agent	Advantages	Disadvantages
Olysio (simeprevir)	• Recommended as part of primary treatment regimen in combination with Sovaldi for select GT1 patients	• Not recommended in patients with HCV GT1a with a nonstructural 3 Q80K polymorphism • When coadministered with sofosbuvir and amiodarone, serious symptomatic bradycardia may occur
Sovaldi (sofosbuvir)	• FDA-approved for HCV GT1, 2, 3, or 4 • Recommended treatment regimen for multiple patient populations (e.g., TN, TE, or HCV/HIV coinfection)	• Must be used in combination with PEG IFN/RBV for GT4 per FDA-approval • Potential bradycardia with concurrent amiodarone administration
Technivie (ombitasvir/ paritaprevir/ritonavir)	• No dosage adjustment required for patients renal impairment	• Only indicated in GT4 • Contraindicated in patients with moderate to severe hepatic impairment • Must be used with RBV • Not studied in patients on dialysis • Not indicated for patients with HIV co-infection
Viekira Pak (ombitasvir/paritaprevir/ ritonavir + dasabuvir) and Viekira XR (dasabuvir/ombitasvir/ paritaprevir/ritonavir ER)	• Recommended treatment regimen for multiple patient populations (e.g., TN, TE, HIV/HCV co-infection, CKD with hemodialysis, post-liver transplant) • ER formulation allows for three tablets once daily administration	• Contraindicated in patients with moderate to severe hepatic impairment • Two tablets in the morning and one table twice daily (Viekira Pak) • Only indicated in GT1
Vosevi (sofosbuvir/velpatasvir/v oxilaprevir)	• First DAA FDA-approved for patients with HCV GT1 through 6 and experienced with NS5A inhibitor therapy with or without compensated cirrhosis • Also FDA-approved for patients with HCV GT1a and GT3 who have been previously treated with sofosbuvir without an NS5A inhibitor • One tablet orally daily with food	• Not indicated in treatment-naïve patients • Coadministration with amiodarone may result in serious, symptomatic bradycardia • Not indicated for patients with HIV co-infection
Zepatier (elbasvir/ grazoprevir)	• One tablet daily with or without food • Recommended treatment regimen for multiple patient population groups (e.g. TN, TE, or HCV/HIV co-infection, CKD with hemodialysis)	• Contraindicated in patients with severe hepatic impairment • Only indicated in GT 1 and GT4

AASLD = American Association for the Study of Liver Diseases
CKD = chronic kidney disease
CYP = cytochrome P450 isoenzyme system
DAA = direct-acting antiviral
ER = extended release
FDA = Food and Drug Administration
GT = genotype
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus
IDSA = Infectious Diseases Society of America
IFN = interferon alfa
NS = nonstructural protein
OATP = organic anion transporting polypeptides
P-gp = P-glycoprotein
PEG= peginterferon
PI = protease inhibitor
RBV = ribavirin
TE = treatment experienced
TN = treatment naïve

FORMULARY CONSIDERATIONS

Mavyret (glecaprevir/pibrentasvir) is the first FDA-approved treatment of eight weeks duration for GT1 through 6 HCV infection in treatment naive patients without compensated cirrhosis as well as in patients with GT1, 2, 4, 5, or 6 infection who are treatment experienced with peginterferon, ribavirin, and/or Sovaldi (sofosbuvir) without cirrhosis. Mavyret (glecaprevir/pibrentasvir) is also the first pan-genotypic FDA-approved HCV treatment to offer a therapy option for patients with chronic kidney disease (CKD), including those on dialysis. In addition, Mavyret (glecaprevir/pibrentasvir) is the first and only agent approved for HCV GT1 patients who are treatment experienced with NS3/4A PIs and serves as an additional treatment option for patients with HCV GT1 who are treatment experienced with NS5A inhibitors. Results from several pivotal clinical trials demonstrated high rates of SVR12 with the administration of Mavyret (glecaprevir/pibrentasvir) in treatment naïve or experienced patients with or without cirrhosis across all six major genotypes of HCV, including patients with CKD. Mavyret (glecaprevir/pibrentasvir) was also shown to have high SVR12 rates in patients with HCV GT1 who had previously been treated with an NS5A inhibitor or an NS3/4A PI. Of note, Mavyret (glecaprevir/pibrentasvir) has a warning for the risk of HBV reactivation. The most common adverse events associated with Mavyret (glecaprevir/pibrentasvir) include headache and fatigue. Overall, Mavyret (glecaprevir/pibrentasvir) was shown to be safe and efficacious as a pan-genotypic agent for HCV in treatment naïve or experienced patients with or without cirrhosis.

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DRUG MONOGRAPH PREPARED BY:

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September 22, 2017

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Pharmacy &Therapeutics Committee Summary Review

Mylotarg® (Gemtuzumab Ozogamicin) – Wyeth Pharmaceuticals Inc

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 3/8/2017

Therapeutic Class: CD33-directed antibody-drug conjugate

FDA Approval Date: 9/7/2017

FDA Indication: Newly-diagnosed CD33-positive acute myeloid leukemia; Relapsed or refractory CD33-positive AML in adults in pediatric patients 2 years and older

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:

Mylotarg was originally approved by the FDA in 2000 and withdrew from the market after trials demonstrating lack of efficacy and increased safety concerns. New FDA approval includes a lower recommended dose, new dosing regimen, and approval for use in a new patient population. The 2017 NCCN Clinical Practice Guidelines in Oncology for AML have not been updated to include Mylotarg. Mylotarg is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Mylotarg™ (gemtuzumab ozogamicin) intravenous injection
Wyeth Pharmaceuticals, Inc.

INDICATIONS

Mylotarg (gemtuzumab ozogamicin) is indicated the treatment of newly-diagnosed cluster of differentiation (CD)33-positive acute myeloid leukemia (AML) in adults, and for the treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients two years of age and older.

KEY POINTS

Mylotarg (gemtuzumab ozogamicin) is a CD33-directed antibody-drug conjugate that was originally approved by the Food and Drug Administration (FDA) under an accelerated approval in 2000 as a single-agent therapy for adult patients with CD33-positive AML who had experienced a relapse (FDA, 2017). The manufacturer later voluntarily withdrew Mylotarg (gemtuzumab ozogamicin) from the market after confirmatory trials demonstrated a lack of efficacy and increased safety concerns. The FDA-approval of Mylotarg (gemtuzumab ozogamicin) on September 1, 2017 under a biologics license application (BLA) includes a lower recommended dose, a new dosing regimen as both a single-agent in combination with chemotherapy, and approval for use in a new patient population, for which Mylotarg (gemtuzumab ozogamicin) received an orphan drug designation.

AML is a cancer that affects immature blood-forming cells found in bone marrow and blood (National Cancer Institute [NCI], 2017a). It is estimated that 21,380 new cases of AML will be diagnosed in the United States in 2017, and there will be 10,590 deaths due to AML (NCI, 2017b). AML is typically diagnosed in older individuals with a median age of diagnosis of 68 years. Treatment for AML is divided into two phases, a remission induction phase to attain remission and a postremission, or consolidation, phase (NCI, 2017a). Complete remission (CR) is typically attained in 60% to 70% of patients following appropriate induction therapy, with more than 25% of patients expected to survive three years or more.

CLINICAL EFFICACY

Combination Therapy in Newly-Diagnosed CD33-positive de novo AML

The safety and efficacy of Mylotarg (gemtuzumab ozogamicin) were evaluated in the Acute Leukemia French Association (ALFA)-0701 study, which was a phase III, open-label, randomized trial conducted in previously untreated patients with de novo AML who were 50 years to 70 years of age (N = 278; Evidence level Ib) (Castaigne, 2012). Though not required, 90% of patients expressed CD33. Patients were excluded from the trial if they had previous myeloproliferative or myelodysplastic syndrome, or exposure to chemotherapy or radiotherapy. Included patients were randomized to receive standard induction therapy with daunorubicin 60 mg/m^2 on days one to three and cytarabine 200 mg/m^2 as continuous infusion for seven days (n = 139) or standard induction therapy plus Mylotarg (gemtuzumab ozogamicin) 3 mg/m^2 (maximum dose of 5 mg) administered over two hours on days one, four, and seven (n = 139). Patients who did not achieve a response following induction received a second induction with daunorubicin and cytarabine alone. Patients with a response received two courses of consolidation therapy: daunorubicin 60 mg/m^2 on day one of first course and days one and two of second course, cytarabine 1 g/m^2 every 12 hours on day one and four of both courses, with or without Mylotarg (gemtuzumab ozogamicin) 3 mg/m^2 (maximum dose of 5 mg) on day one according to initial randomization. The primary endpoint for the trial was event-free survival (EFS), measured as the time from randomization until induction failure (failure to achieve CR or CR with incomplete platelet recovery [CRp]), relapse, or death by any cause. Patients who received Mylotarg (gemtuzumab ozogamicin) in addition to standard therapy had a greater median EFS of 15.6 months (95% confidence interval [CI] 11.7 to 22.4) compared with 9.7 months (95% CI 8.0 to 11.9) in those who received standard therapy, with a hazard ratio (HR) of 0.58 (95% CI 0.43 to 0.78, p = 0.0003).

An updated analysis of the ALFA-0701 study demonstrated continued benefit of treatment with Mylotarg (gemtuzumab ozogamicin) (Castaigne, 2014). After a follow-up ranging from 30 months to 63.5 months, a final analysis in alive patients found an estimated three-year EFS of 19% in patients who received standard therapy compared with 31% in patients who received add-on therapy with Mylotarg (gemtuzumab ozogamicin) (HR 0.66; 95% CI 0.50 to 0.87, p = 0.0026). There was no significant difference in three-year overall survival (OS) (36% vs. 44, respectively; p = 0.18).

Single-Agent Therapy in Newly-Diagnosed CD33-positive AML

The use of Mylotarg (gemtuzumab ozogamicin) as a single-agent therapy in newly-diagnosed patients was evaluated in the AML-19 trial (Amadori, 2016). The AML-19 trial was a phase III, open-label, randomized trial in previously untreated patients with de novo AML or AML secondary to myelodysplasia, who were at least 61 years of age and were ineligible or unwilling to receive standard chemotherapy (N = 237; Evidence level Ib). The median age of patients in the trial was 77 years, and 30.8% of patients had secondary AML. Patients were randomized to receive Mylotarg (gemtuzumab ozogamicin) in addition to best supportive care (BSC) (n = 118) or BSC alone (n = 119). Therapy with Mylotarg (gemtuzumab) included a single induction course of Mylotarg (gemtuzumab ozogamicin) 6 mg/m^2 on day one and 3 mg/m^2 on day eight, followed by up to eight monthly infusions of 2 mg/m^2 if patient demonstrated benefit. BSC consisted of blood product transfusions, antimicrobials, and other symptomatic therapies according to institutional policies. Treatment with hydroxyurea was permitted in the BSC group only to keep white blood cell counts down. The primary endpoint for the trial was OS, in which patients receiving Mylotarg (gemtuzumab ozogamicin) had a longer OS of 4.9 months (95% CI 4.2 to 6.8) compared with 3.6 months (95% CI 2.6 to 4.2) for patients in the BSC group (HR 0.69; 95% CI 0.53 to 0.90, p = 0.005).

Single-Agent Therapy in Relapsed or Refractory CD33-positive AML

Treatment of patients with relapsed or refractory AML with Mylotarg (gemtuzumab ozogamicin) was evaluated in a phase II, open-label, single-arm trial in adult patients with CD33-positive AML in first relapse (N = 57; Evidence level IIa) (Taksin, 2007). The trial excluded patients with secondary leukemia or those who received a previous stem cell transplantation. Treatment included induction therapy with Mylotarg (gemtuzumab ozogamicin) 3 mg/m^2 on days one, four, and seven administered over two hours; followed by consolidation therapy in patients with CR or CRp consisting of cytarabine 3 g/m^2 for patients younger than 55 years of age, and 1 g/m^2 for patients 55 years or older and/or patients with a creatinine clearance less than 50 mL/minute, administered every 12 hours for three days. The overall response rate for patients in the trial, defined as patients who achieved CR and CRp, was 33.3%, including 26% of patients achieving CR. The median relapse-free remission for patients who achieved CR was 11.6 months demonstrating the efficacy of Mylotarg (gemtuzumab ozogamicin) in patients who experience a first relapse following treatment for AML.

SAFETY

Mylotarg (gemtuzumab ozogamicin) has a boxed warning for hepatoxicity, including severe or fatal hepatic veno-occlusive disease. Mylotarg (gemtuzumab ozogamicin) is contraindicated in patients with a hypersensitivity to Mylotarg (gemtuzumab ozogamicin) or any of its components, and there is a related warning and precaution for infusion related reactions, including anaphylaxis. Additional warnings and precautions for Mylotarg (gemtuzumab ozogamicin) include severe or fatal hemorrhage, QT interval prolongation, lack of improvement in event-free survival in AML patients with adverse-risk cytogenetics, and embryo-fetal toxicity. Commonly reported adverse events in all patients receiving Mylotarg (gemtuzumab ozogamicin) with an incidence of 15% or greater included hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased aspartate aminotransferase and/or alanine transferase, rash, and mucositis.

PRODUCT AVAILABILITY

Mylotarg (gemtuzumab ozogamicin) launched on September 9, 2017 (RxPipeline, 2017). Mylotarg (gemtuzumab ozogamicin) is available as 4.5 mg single-dose vials for reconstitution and further dilution for intravenous injection. Vials should be stored in the original carton to protect from light, under refrigeration. Applicable special handling and disposal procedures should be followed when handling Mylotarg (gemtuzumab ozogamicin) since it is a cytotoxic drug.

DOSAGE AND ADMINSTRATION

Patients should be premedicated with a corticosteroid, antihistamine, and acetaminophen one hour prior to the administration of Mylotarg (gemtuzumab ozogamicin) in order to prevent infusion related reactions. Recommended dosages for Mylotarg (gemtuzumab ozogamicin) are outlined in Table 1.

Table 1: Recommended Dosing Regimens for Mylotarg (gemtuzumab ozogamicin)

Diagnosis	Dosing Regimen
Newly-diagnosed, de novo AML (combination regimen)	Induction: 3 mg/m^2 (up to one 4.5 mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine Consolidation: 3 mg/m^2 on day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine
Newly-diagnosed AML (single-agent regimen)	Induction: 6 mg/m^2 on day 1, and 3 mg/m^2 on day 8 Continuation*: 2 mg/m^2 on day 1 every 4 weeks
Relapsed or refractory AML (single-agent regimen)	3 mg/m^2 on days 1, 4, and 7

* For patients without evidence of disease progression following induction, up to eight consecutive courses of treatment
AML = acute myeloid leukemia

PLACE IN THERAPY

- Mylotarg (gemtuzumab ozogamicin) is an intravenous infusion that is indicated as an add-on therapy to standard chemotherapy in newly-diagnosed patients with de novo AML, or as monotherapy in patients with newly-diagnosed, relapsed, or refractory AML.
- According to National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia, standard therapies for patients with AML have changed little in the past 40 years and includes cytarabine plus an anthracycline, with daunorubicin commonly used (NCCN®, 2017). The guidelines were not updated since the approval of Mylotarg (gemtuzumab ozogamicin).
- The reduced dose and new dosing regimen of Mylotarg (gemtuzumab ozogamicin) appears to provide greater EFS and OS in newly-diagnosed patients with AML as both add-on therapy to standard chemotherapy and as a single-agent therapy compared with standard chemotherapy or BSC alone. However, therapy with Mylotarg (gemtuzumab ozogamicin) was associated with a greater incidence of hematologic adverse events. Monotherapy with Mylotarg (gemtuzumab ozogamicin) also demonstrated response in patients with relapsed or refractory AML.

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Data were compiled using the prescribing information of [Brand (generic)] unless otherwise notated

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National Comprehensive Cancer Network®. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia, V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed August 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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CONDENSED DRUG MONOGRAPH PREPARED BY:

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September 22, 2017

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

Pharmacy &Therapeutics Committee Summary Review

Nerlynx® (neratinib) – Puma Biotechnology, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 3/8/2017

Therapeutic Class: Kinase Inhibitor

FDA Approval Date: 7/17/2017

FDA Indication: Extended adjuvant treatment of adult patients with early state HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:

Nerlynx is the first agent approved for the extended adjuvant treatment of HER2-positive breast cancer following adjuvant therapy with Herceptin. Clinicals showed that patients with early stage HER2-positive breast cancer receiving treatment with Nerlynx for 12 months following therapy with Herceptin improved iDFS at 2 years compared with placebo. Nerlynx is recommended as a non-preferred product and will be approved for FDA approved indications only to allow for approval of studied diagnoses and patient populations.

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CVS Caremark Pharmacy & Therapeutics Drug Monograph

Nerlynx™ (neratinib) tablets
Puma Biotechnology, Inc.

INDICATION

Nerlynx (neratinib) is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth receptor 2 (HER2)-overexpressed/amplified breast cancer, to follow adjuvant Herceptin (trastuzumab)-based therapy (Nerlynx prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Nerlynx (neratinib) was approved by the FDA on July 17, 2017 with a review designation of 1S (FDA, 2017a). Nerlynx (neratinib) is a new molecular entity that underwent standard review.

DRUG SUMMARY

Nerlynx (neratinib)	
Place in Therapy	• Nerlynx is the first agent approved for the extended adjuvant treatment of HER2-positive breast cancer following adjuvant therapy with Herceptin (trastuzumab). • Herceptin is recommended for adjuvant therapy in HER2-positive breast cancer for up to one year, and treatment up to two years did not provide additional benefit in outcomes. • Up to 26% of patients may develop recurrent disease despite adjuvant treatment with Herceptin.
Efficacy	• The efficacy and safety of Nerlynx were evaluated in a phase III, randomized, double-blind, placebo-controlled trial in adult women with HER2-positive breast cancer who had completed adjuvant therapy with Herceptin. • After a median follow-up of 24 months, adjuvant treatment with Nerlynx for 12 months following therapy with Herceptin reduced the number of invasive disease-free survival events compared with placebo (70 vs. 109; stratified HR 0.67, 95% CI 0.50 to 0.91; p = 0.0091)
Safety	• Warnings and precautions: diarrhea, hepatotoxicity, and embryo-fetal toxicity • Common adverse events (> 5%): diarrhea, nausea, abdominal pain, fatigue, vomiting, rash stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased, and urinary tract infection

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CI = confidence interval
HER2 = human epidermal growth receptor 2
HR = hazard ratio

CLINICAL PHARMACOLOGY

Mechanism of Action

Neratinib is an irreversible kinase inhibitor of epidermal growth factor receptor (EGFR), HER2, and HER4 (Nerlynx prescribing information, 2017). Inhibition of these kinases by neratinib and its metabolites have demonstrated antitumor activity in EGFR- and/or HER2- expressing carcinoma cell lines.

CLINICAL EFFICACY

Table 2: Efficacy of Nerlynx (neratinib) in the Extended Adjuvant Treatment of HER2-positive Breast Cancer

<table>
<tr><th>Study, Treatments, and Groups</th><th>Study Design and Endpoints</th><th>Study Criteria</th><th colspan="5">Results</th></tr>
<tr><td rowspan="5">ExteNET;
Chan, 2016
Evidence Level Ib
Nerlynx 240 mg
once daily for
12 months
(n = 1,420)
vs.
Placebo
once daily for
12 months
(n = 1,420)</td><td rowspan="5">N = 2,840
Study Design:
Phase III, randomized, double-blind, placebo-controlled trial
Objective:
To evaluate the efficacy of extended adjuvant anti-HER2 treatment with Nerlynx after Herceptin (trastuzumab)-based therapy in patients with HER2-positive breast cancer
Primary Endpoint:
iDFS* at 2 years
Secondary Endpoint:
DFS including ductal carcinoma in situ</td><td rowspan="5">Inclusion Criteria:
• Women ≥ 18 years of age† with stage 1 to 3 HER2-positive breast cancer who had completed Herceptin therapy up to 2 years before randomization (median age 52 years; 81% Caucasian)
• Amended to include higher risk patients defined as those with stage 2 to 3 HER2-positive breast cancer who had completed Herceptin therapy up to 1 year previously
Exclusion Criteria:
• Clinically significant gastrointestinal, cardiac, or psychiatric comorbidities
• Patients unable to swallow oral drugs</td><td>Endpoint</td><td>Nerlynx
(n = 1,420)</td><td>Placebo
(n = 1,420)</td><td>Hazard Ratio</td><td>p-value</td></tr>
<tr><td>Number of iDFS events (95% CI)</td><td>70</td><td>109</td><td>0.67‡
(0.50 to 0.91)</td><td>0.0091</td></tr>
<tr><td>iDFS rate (95% CI)</td><td>93.9%
(92.4 to 95.2)</td><td>91.6%
(90.0 to 93.0)</td><td>—</td><td>—</td></tr>
<tr><td>DFS including ductal carcinoma in situ (95% CI)</td><td>93.9%
(92.4 to 95.2)</td><td>91.0%
(89.3 to 92.5)</td><td>0.63
(0.46 to 0.84)</td><td>0.0017</td></tr>
<tr><td colspan="5">A subgroup analysis in patients with hormone receptor-positive breast cancer (n = 1,631) found Nerlynx provided greater iDFS compared with placebo (hazard ratio 0.51; 95% CI 0.33 to 0.77; p = 0.0013). No statistically significant difference was observed in patients with hormone receptor-negative breast cancer (hazard ratio 0.93; 95% CI 0.60 to 1.43; p = 0.74).
Safety
• The most commonly reported grade 3 treatment-emergent adverse event in patients receiving Nerlynx was diarrhea (40%). One patient experienced grade 4 diarrhea. Diarrhea tended to occur early in treatment (within first month) and decreased substantially over time. Diarrhea led to discontinuation in 17% of patients receiving Nerlynx after a median time of 20 days compared with < 1% of patient in the placebo group.
• There were no significant differences observed between Nerlynx and placebo for QT prolongation (3% vs. 7%) or decreases in left ventricular ejection fraction (≥ grade 2) (1% for each).
• Four deaths in the Nerlynx group and three deaths in the placebo group unrelated to disease progression occurred after study discontinuation, which were all determined not to be attributed to study treatment.
Comments/Study Limitations: Concurrent adjuvant endocrine therapy was recommended for patients with hormone receptor-positive disease. Antidiarrheal prophylaxis was not specified in the study protocol.
Conclusions: In patients with early stage HER2-positive breast cancer, extended adjuvant treatment with Nerlynx for 12 months following therapy with Herceptin improved iDFS at 2 years compared with placebo.</td></tr>
</table>

* Defined as the time between date of randomization to the first occurrence of invasive disease including invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause
† ≥ 20 years of age in Japan
‡ Stratified hazard ratio; patients were stratified based on hormone receptor status, nodal status, and prior Herceptin adjuvant regimen
CI = confidence interval
DFS = disease-free survival
HER2 = human epidermal growth receptor 2
iDFS = invasive disease-free survival

(Chan, 2016)

Drug Interactions

Table 3: Potential Drug Interactions with Neratinib

Interacting Agent	Outcome	Recommendation
Gastric Acid Reducing Agents	Decreased exposure to neratinib; potential decreased efficacy of Nerlynx (neratinib)	Avoid concomitant use with proton pump inhibitors (PPIs) and H2-receptor antagonists; separate dosing with antacids by 3 hours after administration of antacid
Strong and Moderate CYP3A4 Inhibitors	Increased exposure to neratinib; increased risk of adverse events	Avoid concomitant use
Strong and Moderate CYP3A4 Inducers	Decreased exposure to neratinib; potential decreased efficacy of Nerlynx (neratinib)	
P-gp substrates	Potential increased exposure to P-gp substrate	Monitor for adverse events of narrow therapeutic agents that are P-gp substrates (e.g., digoxin) when used concomitantly

CYP = cytochrome P450
P-gp = P-glycoprotein

(Nerlynx prescribing information, 2017)

Adverse Events

Table 4: Adverse Events for Nerlynx (neratinib) with an Incidence of 5% or More in the Pivotal Clinical Trial

Adverse Event	Nerlynx (n = 1,408)		Placebo (n = 1,408)	
	All Grades	Grade 3	All Grades	Grade 3
Diarrhea	95%	40%	35%	2%
Nausea	43%	2%	22%	0.1%
Abdominal pain	36%	2%	15%	0.4%
Fatigue	27%	2%	20%	0.4%
Vomiting	26%	3%	8%	0.4%
Rash	18%	0.6%	9%	0%
Stomatitis	14%	0.6%	6%	0.1%
Decreased appetite	12%	0.2%	3%	0%
Muscle spasms	11%	0.1%	3%	0.1%
Dyspepsia	10%	0.4%	4%	0%
Alanine aminotransferase increased	9%	1%	3%	0.2%
Nail disorder	8%	0.3%	2%	0%
Aspartate aminotransferase increased	7%	0.5%	3%	0.3%
Dry skin	6%	0%	2%	0%
Abdominal distension	5%	0.3%	3%	0%
Urinary tract infection	5%	0.1%	2%	0%
Weight decreased	5%	0.1%	0.5%	0%
Epistaxis	5%	0%	1%	0.1%

(Nerlynx prescribing information, 2017)

PRODUCT AVAILABILITY

Nerlynx (neratinib) is available as a 40 mg oral tablet in bottles of 126 tablets or 180 tablets (Nerlynx prescribing information, 2017). Nerlynx (neratinib) launched on July 27, 2017 (RxPipeline, 2017).

The most common symptom of breast cancer is a new lump or mass (ACS, 2017). A painless mass that is hard and has irregular edges are the most common signs for breast cancer, but masses can be painful, soft, or rounded. Swelling of the breast, skin irritation or dimpling, nipple retraction, redness, scaliness, thickening of the nipple or breast skin, and discharge from the nipple are other possible symptoms associated with breast cancer. If breast cancer has spread to surrounding lymph nodes under the arm or around the collar bone, a lump or swelling in these areas may be apparent before the tumor in the breast is large enough to be detected.

Once the diagnosis of breast cancer is established, the tumor is staged in order to serve as a guide to treatment and to determine prognosis (ACS, 2017; NCCN, 2017). Similar to other solid tumors, breast cancer is staged according to the tumor-node-metastasis (TNM) classification system developed by the American Joint Committee on Cancer. Staging is categorized as stages I through IV, with the higher number representing more advanced stages, and based on the extent of the primary tumor, absence or presence of metastasis to nearby lymph nodes, and the absence or presence of distant metastasis. The five-year survival for stages 0 or I is close to 100% and decreases to only 22% for stage IV with current treatments.

Prognosis and the selection of local (e.g., surgery and/or radiation therapy) therapies or systemic (e.g., chemotherapy, endocrine therapy, biologic therapy, or a combination of these therapies) therapies for the treatment of breast cancer are dependent on several prognostic and predictive factors (NCCN, 2017). Prognostic and predictive factors include tumor histology, clinical and pathological characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor (estrogen receptor [ER]/ progesterone receptor [PR]) status, HER2 tumor status multi-gene testing, the presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status.

In addition to staging, diagnosis of breast cancer also should include determining biologic features of the tumor based on pathological examination of a biopsy (NCCN, 2017). This includes histological typing, ER status for all tumors, PR status for invasive tumors, and HER2 status for all newly diagnosed invasive tumors and for tumor recurrences. Approximately two-thirds of breast cancer is ER and/or PR positive, while approximately 20% is HER2 positive (ACS, 2017). ER/PR positive tumors are more common in older women. Hormone receptor-positive cancers are more common in postmenopausal women and are associated with an improved response to hormonal therapies. Hormone receptor-positive cancers are usually less aggressive with a better short-term outlook but are more likely to relapse many years after treatment.

Treatment

Treatment recommendations for breast cancer are complex and depend on a wide range of factors including tumor histology, disease stage, previous therapy, ER and/or PR tumor status, HER2 status, menopausal status, comorbid disease states, and patient preference (NCCN, 2017). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend surgery with or without radiation therapy for the treatment of early stage (stage I through IIIA) invasive breast cancer. Adjuvant systemic therapy should be considered based on the risk for relapse and the primary characteristics of the tumor including the tumor size, grade, lymph node involvement, ER/PR status, and HER2-receptor expression, without regard to a patient's age. In patients with HER2-positive tumors, NCCN Guidelines® recommend adjuvant therapy with combinations of endocrine therapy and chemotherapy dependent on additional tumor characteristics, in combination with the HER2-targeted therapy trastuzumab (Herceptin) for one year, which has demonstrated significant improvement in disease free survival. However, up to 26% of patients may experience recurrent disease following adjuvant therapy (Chan, 2016). The use of trastuzumab (Herceptin) as adjuvant therapy beyond one year is not recommended due to no difference in outcomes compared with adjuvant therapy for up to two years (NCCN, 2017). Nerlynx (neratinib) is the first agent FDA-approved as extended adjuvant therapy in patients with HER2-positive breast cancer and has not yet been evaluated for inclusion in guidelines (FDA, 2017b; NCCN, 2017).

DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS
September 22, 2017

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

Pharmacy &Therapeutics Committee Summary Review

Siliq® (brodalumab) - Valeant Pharmaceuticals North America LLC

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2018

Therapeutic Class: Human interleukin-17 receptor A (IL-17RA) antagonist

FDA Approval Date: 2/15/2017

FDA Indication: Plaque Psoriasis

Comparable Products: Taltz (non-preferred), Cosentyx (non-preferred), Stelara (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred

- For initial authorization:
  - Member must be 18 years of age or older; AND
  - Member must have a documented negative TB test (i.e. tuberculosis skin test (PPD), an interferonrelease assay (IGRA), or a chest x-ray) within 6 months prior to starting therapy; AND
  - Medication must be prescribed by a dermatologist or rheumatologist; AND
  - Member has PP for 6 months or longer; AND
  - Member is not going to receive systemic therapy or phototherapy while on Siliq; AND
  - Member's PP involving 10% or more of the body surface area (BSA) or 5% or more of BSA if psoriasis involves sensitive areas (hands, feet, face, or genitals); AND
  - Member's Psoriasis Area and Severity Index (PASI) score ≥12; AND
  - Member's static Physician's Global Assessment (sPGA) score ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling); AND
  - Member must not have a diagnosis for Crohn's Disease; AND
  - Documented consultation on risks of suicidal ideation or behavior while on Siliq is submitted with member's chart notes AND
  - Member has tried and failed to respond to treatment with at least one of the following:
    - At least 12 weeks of photochemotherapy (i.e. psoralen plus ultraviolet A therapy);
    - At least 12 weeks of phototherapy (i.e. UVB light therapy, Excimer laser treatments (tanning beds emit mostly UVA light and therefore would not meet this criteria));
    - At least a 4 week trial with topical antipsoriatic agents (i.e. anthralin, calcipotriene, coal tar, corticosteroids, tazarotene); AND
  - Member has tried and failed to respond to treatment of an immunosuppressant (i.e. cyclosporine, methotrexate, acetretin) for at least a 12 week trial; AND
  - Member has tried and failed to respond to treatment with both Enbrel and Humira.
  - Dosage allowed: 210 mg subcutaneously once weekly at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
- For reauthorization:
  - Member must have been retested for TB with a negative result within the past 12 months; AND
  - Member must be in compliance with all other initial criteria; AND
  - Chart notes have been provided that show the member has shown improvement of signs and symptoms of disease; AND
  - Documented member's PASI score improvement; AND
  - Documented member's sPGA score improvement.

Clinical Implications/ Place in Therapy:

New drug for Plaque Psoriasis was reviewed. Criteria for Siliq are written based on trials data from drug's package insert and guideline consensus for the plaque psoriasis. Non-preferred drug status is recommended.

References:

1. Siliq [prescribing information]. Bridgewater, NJ; Valeant Pharmaceuticals North America LLC. Revised February 2017.
2. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012 Jan;148(1):95-102.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Siliq™ (brodalumab) subcutaneous injection Valeant Pharmaceuticals, Inc.

INDICATION

Siliq (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies (Siliq prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Siliq (brodalumab) was approved by the FDA on February 15, 2017 under a Biologics License Application (BLA) (FDA, 2017a).

DRUG SUMMARY

Siliq (brodalumab)	
Place in Therapy	• Siliq serves as an additional biologic therapy available for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy and have failed to respond to other systemic therapies. • The American Academy of Dermatology (AAD) guidelines for the treatment of psoriasis recommend phototherapy, PUVA, methotrexate, oral cyclosporine, oral retinoids (acitretin), and biologic agents for the treatment of moderate to severe psoriasis. No specific biologic agents are recommended in the guidelines. • Several biosimilars to currently available TNF-α antagonist therapies for plaque psoriasis have been approved and are expected to be launched in the coming years.
Efficacy	• FDA approval of Siliq was based on one 52-week phase III, randomized, placebo-controlled trial (N = 661) and two 52-week, phase III, randomized, placebo-controlled, and active comparator-controlled trials (N = 1,831; N = 1,881) demonstrating 85% to 86% of Siliq-treated patients achieving at least a 75% reduction in PASI score and 79% to 80% of patients achieving skin improvement to "clear" or "almost clear" or sPGA score of 0 or 1. • In the active comparator trials, Siliq also demonstrated superiority compared with Stelara (ustekinumab) at week 12 in achieving PASI 100 response and skin improvement to "clear" or "almost clear".
Safety	• Boxed warning: suicide ideation and behavior • Available only through Siliq REMS program • Contraindication: Crohn's disease • Similar to other biologic therapies in the class, Siliq has the following warnings and precautions: risks of serious infection, tuberculosis, Crohn's disease, and administration of live vaccines • Common adverse events (1% to 5%): arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections

FDA = Food and Drug Administration
PASI = Psoriasis Area and Severity Index
PASI 100 = 100% reduction from baseline in PASI score
PUVA = psoralen and ultraviolet A light
REMS = Risk Evaluation and Mitigation Strategies
sPGA = static Physician's Global Assessment
TNF = tumor necrosis factor

CLINICAL EFFICACY

Table 2: Efficacy of Siliq (brodalumab) on Treatment of Moderate to Severe Plaque Psoriasis

Study (Evidence Level Ib)		**AMAGINE-1** (N = 661) Papp, 2016			**AMAGINE-2 and AMAGINE-3** (N = 1831; N = 1881) Lebwohl, 2015							
Design*		Phase III, randomized, double-blind, placebo-controlled, multinational, 52-week trial with 12-week induction phase										
Inclusion Criteria		Patients aged 18 to 75 years (mean age 45 to 47 years, 68% to 74% male) with stable moderate-to-severe plaque psoriasis ≥ 6 months before the first dose of treatment; psoriasis affected body surface area ≥ 10%, PASI† ≥ 12 and sPGA† ≥ 3; negative pregnancy test, no known history of active tuberculosis, and negative for tuberculosis during screening and baseline.										
Exclusion Criteria:		Diagnosed with skin conditions that would interfere with the interpretation of results; active infection within 28 days or history of serious infection within 8 weeks; history of Crohn disease, hepatitis B, hepatitis C or human immunodeficiency virus; myocardial infarction or unstable angina pectoris within 12 months; active malignancy or a history of malignancy within 5 years; any systemic disease considered to be clinically significant and uncontrolled.										
Treatment‡		**Siliq 210 mg SC Q2W** (n = 222)	**Siliq 140 mg SC Q2W** (n = 219)	**Placebo** (n = 220)	**Siliq 210 mg SC Q2W** (n = 612)	**Siliq 140 mg SC Q2W** (n = 610)	**Stelara (ustekinumab)** (n = 300)	**Placebo** (n = 309)	**Siliq 210 mg SC Q2W** (n = 624)	**Siliq 140 mg SC Q2W** (n = 629)	**Stelara (ustekinumab)** (n = 313)	**Placebo** (n = 315)
Results	% of patients with PASI 75 at week 12§	83.3¶	60.3¶	2.7	86¶	67¶	70	8	85¶#	69¶	69	6
	% of patients with sPGA 0 or 1 at week 12§	75.7¶	53.9¶	1.4	79¶#	58¶	61	4	80¶#	60¶	57	4
	% of patients with PASI 100 at week 12‖	41.9¶	23.3¶	0.5	44¶#	26¶	22	1	37¶#	27¶#	19	0.3
	% of patients with sPGA 0 at week 12‖	41.9¶	23.3¶	0.5	45¶#	26¶	22	1	37¶#	27¶#	19	0.3
	% of patients with PSI response at week 12‖	60.8¶	53.0¶	4.1	68¶	51¶	55	7	61¶	53¶	52	6
Safety		The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Candida infections were more frequent in Siliq groups than in the Stelara and placebo groups. The rates of serious adverse events through 52 weeks were 7.9 to 9.5 per 100 patient-years; the exposure-adjusted event rate for suspected Candida infection was 3.5 per 100 patient-years. Slightly more neutropenia and suicide attempts were seen in Siliq groups than in the Stelara and placebo groups. In AMAGINE-1, 73% to 77% of Siliq-treated patients experienced improved HADS depression score compared to 45% of placebo-treated patients. The exposure-adjusted depression rates were 1.7% for Siliq and 3.3% for Stelara in AMAGINE-2 and 1.8% for Siliq and 0.8% for Stelara in AMAGINE-3.										
Comments		In AMAGINE-2, the three events of suicide attempts occurred in one individual receiving Siliq 210 mg with the first event occurred during the 12 week induction phase. One completed suicide occurred 27 days after the last dose of brodalumab 210mg. In AMAGINE-3, Siliq 140 mg showed statistically significant benefit over Stelara at achieving PASI 100 and sPGA 0 at week 12. The median time to achieve a PASI 75 response or sPGA success was 4 weeks.										
Conclusion		Siliq 210 mg SC Q2W was superior to placebo and Stelara at rapidly reducing psoriasis symptoms and producing better PASI 75 and sPGA 0 or 1 response rates.										

* In AMAGINE-1, patients experiencing treatment success at end of 12 weeks were re-randomized to receive Siliq induction dose or placebo (withdrawal phase). In AMAGINE-2 and AMAGINE-3, patients receiving treatment success with closed-label brodalumab at end of 12 weeks were re-randomized to receive one of four brodalumab maintenance regimens.
† PASI score ranges from 0 to 72; PSI score ranges from 0 to 32; sPGA score ranges from 0 to 5; higher number signifies more severe disease
‡ Siliq Q2W also included a dose one week after the first dose.
§ Primary efficacy endpoints
‖ Secondary efficacy endpoints; PSI response defined as a total score of ≤ 8 with no item score > 1
¶ p-value < 0.05 vs. placebo
# p-value < 0.05 vs. Stelara
Evidence Level Ib = randomized, controlled trial
HADS = Hospital Anxiety and Depression Scale
PASI = Psoriasis Area and Severity Index
PASI 75 = 75% or greater reduction from baseline in PASI score
PASI 100 = 100% reduction from baseline in PASI score
PSI = Psoriasis Symptom Inventory
(Lebwohl, 2015; Papp, 2016)
Q2W = every 2 weeks
SC = subcutaneous
sPGA = static Physician's Global Assessment

Warnings and Precautions

Suicidal Ideation and Behavior

Suicidal ideation and behavior, including four completed suicides, occurred in Siliq (brodalumab)-treated patients in the psoriasis clinical trials (Siliq prescribing information, 2017). There were no completed suicides in the 12-week placebo-controlled portion of the trials. Siliq (brodalumab)-treated patients with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to Siliq (brodalumab)-treated patients without such a history. A causal association between treatment with Siliq (brodalumab) and increased risk of suicidal ideation and behavior has not been established. Potential risks and benefits should be evaluated before starting Siliq (brodalumab) in patients with a history of depression and suicidality. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional. Patients and caregivers should be advised to seek medical attention for manifestations of suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes. The risks and benefits of continuing treatment with Siliq (brodalumab) should be re-evaluated if such events occur. Because of the observed suicidal ideation and behavior in Siliq (brodalumab)-treated patients, if an adequate response to Siliq (brodalumab) has not been achieved within 12 to 16 weeks, discontinuation of Siliq (brodalumab) should be considered.

Infections

Siliq (brodalumab) may increase the risk of infections (Siliq prescribing information, 2017). In clinical trials, Siliq (brodalumab)-treated patients compared with placebo-treated patients had higher rates of serious infections (0.5% vs. 0.2%) and higher rates of fungal infections (2.4% vs. 0.9%). One case of cryptococcal meningitis occurred in a patient treated with Siliq (brodalumab) during the 12-week randomized treatment period and led to discontinuation of therapy. During the course of clinical trials for plaque psoriasis, the exposure-adjusted rates for infections and serious infections were similar in the Siliq (brodalumab)-treated patients and Stelara (ustekinumab)-treated patients.

Patients with a chronic infection or a history of recurrent infection should be evaluated for risks and benefits prior to receiving Siliq (brodalumab) (Siliq prescribing information, 2017). Patients should be instructed to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy for the infection, the patient should be closely monitored and Siliq (brodalumab) should be discontinued until the infection resolves.

Risk for Latent Tuberculosis Reactivation

Patients should be evaluated for tuberculosis (TB) infection prior to initiating treatment with Siliq (brodalumab) (Siliq prescribing information, 2017). Siliq (brodalumab) should not be administered to patients with active TB infection. Treatment of latent TB should be initiated prior to administering Siliq (brodalumab). Anti-TB therapy should be considered prior to initiation of Siliq (brodalumab) in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving Siliq (brodalumab) should be monitored closely for signs and symptoms of active TB during and after treatment.

Immunizations

Administration of live vaccines should be avoided in patients treated with Siliq (brodalumab) (Siliq prescribing information, 2017). No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with Siliq (brodalumab).

PRODUCT AVAILABILITY

Siliq (brodalumab) is available as a 210 mg/1.5 mL single-dose prefilled syringe in cartons of two syringes (Siliq prescribing information, 2017). Siliq (brodalumab) must be refrigerated at 2°C to 8°C (36°F to 46°F).

DOSAGE AND ADMINISTRATION

The recommended dose of Siliq (brodalumab) is 210 mg administered by subcutaneous injection at weeks zero, one, and two followed by 210 mg every two weeks (Siliq prescribing information, 2017). If an adequate response has not been achieved after 12 to 16 weeks of treatment with Siliq (brodalumab), discontinuation of therapy should be considered.

APPROACHES TO TREATMENT

Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations (Menter, 2011). Psoriasis may occur at any age, although the majority of cases develop before 40 years of age, and it is uncommon in children. An estimated 7.4 million (2% to 4%) Americans have psoriasis (Rachakonda, 2014). Men and women develop psoriasis at equal rates, and while psoriasis occurs in all racial groups at varying rates, i.e., approximately 1.9% of African-Americans have psoriasis, compared with 3.6% of Caucasians (National Psoriasis Foundation, 2017a). The occurrence of psoriasis is more frequent in countries more distant from the equator (Parisi, 2013).

Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration consisting mostly of T lymphocytes, and various endothelial vascular changes in the dermal layer (e.g., angiogenesis) (Krueger, 2005). The release of interleukin (IL)-17, interleukin (IL)-23 and tumor necrosis factor (TNF)-α by activated immune cells appear to be the principal driver of lesion development and persistence (Boehncke, 2015; Krueger, 2005).

Patients with psoriasis have an increased incidence of lymphoma, heart disease, obesity, type 2 diabetes, and the metabolic syndrome (Menter, 2011). Depression and suicide, smoking, and alcohol consumption are also more common in patients with psoriasis. Severe, chronic psoriasis may be associated with an increased mortality risk, largely due to cardiovascular death (Boehncke, 2015; Menter, 2011).

Several types of psoriatic lesions occur, and each differs slightly and responds differently to treatment (Callen, 2003). Plaque psoriasis, or psoriasis vulgaris, accounts for 80% to 90% of patient cases and is characterized by monomorphic, sharply demarcated erythematous plaques covered by silvery lamellar scales (Boehncke, 2015; Menter, 2008). Although psoriasis can affect any skin site, typical locations include extensor surfaces of forearms and shins, peri-umbilical, perianal, retro-auricular regions and, most commonly, the scalp. The quality of life impact of psoriasis may be large even in patients with small areas of involvement, such as palms and soles.

The diagnosis of psoriasis is usually made on clinical findings (Boehncke, 2015; Langley, 2004). In routine clinical care, the most common tool to quantify disease severity is the Psoriasis Area and Severity Index (PASI) score, which combines the assessment of the severity of lesions and the area affected into a single score ranging from zero (no disease) to 72 (maximal disease). A simpler tool is the physician's global assessment (PGA) for psoriasis, which has a 4-point scale ranging from zero (clear skin) to four (severe, very marked plaque elevation, scaling, and erythema). The present goal in psoriasis treatment is to reduce cutaneous signs and symptoms at least 75% as measured by the PASI score, or to achieve psoriasis covering 3% or less of body surface area (BSA), after three months of treatment, and to guarantee a good quality of life as measured by a Dermatology Life Quality Index (DLQI) score of 5 or less (Boehncke, 2015; National Psoriasis Foundation, 2017b).

Table 5: Comparison of Agents for Treatment of Moderate-to-Severe Plaque Psoriasis

Agent	Advantages	Disadvantages
All Injectable Agents	• May be self-administered subcutaneously, with the exception of Remicade and biosimilars • Generally have higher PASI 75 and sPGA/IGA response rates	• No agents are approved for use in pediatric patients with plaque psoriasis, with the exception of Enbrel • Safety concern: risk of serious infections, malignancy • Cannot be used in immunosuppressed patients • Must be refrigerated
TNF-α Inhibitors		
Enbrel (etanercept)/ Erelzi (etanercept-szzs) SC injection	• Multiple additional FDA-approved indications including AS, JIA, psoriatic arthritis, and RA • Only agent with pediatric plaque psoriasis indication • Longer term safety and efficacy data available • PASI 75 response rates*: 47%	• Boxed warning: serious infections, malignancies (lymphoma); contraindicated in sepsis; safety concerns: skin reactions, demyelinating syndromes, HF, development of autoantibodies resulting in lupus-like syndrome or autoimmune hepatitis • Once-weekly administration
Humira (adalimumab)/ Amjevita (adalimumab-atto) SC injection	• Multiple additional FDA-approved indications including AS, hidradenitis suppurativa, JIA, psoriatic arthritis, RA, UC, uveitis, and Crohn's disease • Longer term safety and efficacy data available • PASI 75 response rates*: 71%	• Boxed warning: serious infections, hepatosplenic T-cell lymphoma; safety concerns: malignancies (lymphoma), demyelinating syndromes, HF • Loss of efficacy may be seen in a small percentage of patients with continued use
Remicade (infliximab)/ Inflectra (infliximab-dyyb)/ Renflexis (infliximab-abda) IV infusion	• Multiple additional FDA-approved indications including RA, AS, psoriatic arthritis, Crohn's disease, and UC • Relatively rapid onset of effect • Longer term safety and efficacy data available • Administered every 8 weeks • PASI 75 response rates*: 75% to 88%	• Boxed warning: serious infections, hepatosplenic T-cell lymphoma; safety concerns: malignancies (lymphoma), demyelinating syndromes, HF, hepatotoxicity, infusion-related reactions • IV administration under controlled health care setting with available medical support • High frequency of antibody development vs. Humira or Enbrel
IL-17A Inhibitors		
Cosentyx (secukinumab) SC injection	• Multiple additional FDA-approved indications including AS and psoriatic arthritis • Demonstrated superiority to Enbrel and Stelara in achieving PASI 75 and response IGA 0/1 response • PASI 75 response rates*: 70% to 87%	• Safety concerns: inflammatory bowel disease • Requires titration up to the recommended administration frequency of once every four weeks
Siliq (brodalumab) SC injection	• Demonstrated superiority to Stelara in achieving PASI 75 and sPGA 0/1 response • PASI 75 response rates*: 85% to 86%	• Boxed warning: suicidal ideation and behavior; available only through Siliq REMS program; contraindicated in Crohn's Disease • Requires titration up to the recommended administration frequency of once every two weeks
Taltz (ixekizumab) SC injection	• Demonstrated superiority to Enbrel in achieving PASI 75 and response IGA 0/1 response • PASI 75 response rates*: 81.6% to 88.7%	• Safety concerns: inflammatory bowel disease • Requires titration up to the recommended administration frequency of once every four weeks
IL-12/23 Inhibitor		
Stelara (ustekinumab) SC injection	• Also indicated for psoriatic arthritis • Clinical response data available for up to 5 years • Administered every 12 weeks • PASI 75 response rates*: 66% to 76%	• Safety concerns: malignancies (lymphoma), Reversible posterior leukoencephalopathy syndrome (RPLS)
PDE-4 Inhibitor		
Otezla (apremilast) oral tablet	• Also indicated for psoriatic arthritis • Oral administration; the only non-biologic agent for treating moderate-to-severe plaque psoriasis • Can be used in immunosuppressed patients • PASI 75 response rates*: 29% to 33%	• Safety concern: depression, weight loss • Loss of efficacy seen with strong cytochrome P450 enzyme inducers • Adverse events (≥ 5%): diarrhea, nausea • Requires titration up to the recommended dose • Twice daily dosing

* Based on change from baseline in clinical trials comparing active control to placebo; results are not collected from comparative trials between biologic agents for psoriasis

AS = ankylosing spondylitis
HF = heart failure
IL = interleukin
IM = intramuscular
IGA = Investigator's Global Assessment
IV = intravenous
JIA = juvenile idiopathic arthritis
PASI = psoriasis area and severity index
PDE = phosphodiesterase
RA = rheumatoid arthritis
REMS = Risk Evaluation and Mitigation Strategies
SC = subcutaneous
sPGA = static Physician's Global Assessment
TNF = tumor necrosis factor
UC = ulcerative colitis

(Prescribing information: Amjevita, 2016; Cosentyx, 2016; Enbrel, 2016; Erelzi, 2017; Humira, 2017; Inflectra, 2016; Otezla, 2014; Remicade, 2015; Renflexis, 2017; Siliq, 2017; Stelara, 2016; Taltz, 2016)

FORMULARY AND DRUG LIST AVAILABILITY

Table 7: Formulary/Drug List Availability of Plaque Psoriasis Agents

Product	National Formulary	Prescribing Guide	Prescribing Guide for Advanced Controlled Specialty Formulary	Performance Drug List	Performance Drug List for Advanced Controlled Specialty Formulary	Advanced Control Formulary	Value Formulary*
Siliq (brodalumab) SC injection	—						
Amjevita (adalimumab-atto) SC injection	—†						
Cosentyx (secukinumab) SC injection	✓	**NTMB**	**Excluded**	**NTMB**	**Excluded**	**Excluded**	—
Enbrel (etanercept) SC injection	✓	✓	—	✓	—	—	—
Erelzi (etanercept-szzs) SC injection	—†						
Humira (adalimumab) SC injection	✓	✓	✓	✓	✓	✓	✓‡
Inflectra (infliximab-dyyb) IV infusion	✓	**NTMB**					—
Otezla (apremilast) oral tablet	✓	—	**Excluded**	—	**Excluded**	**Excluded**	—
Remicade (infliximab) IV infusion	✓	—	**Excluded**	—	**Excluded**	**Excluded**	—
Renflexis (infliximab-abda) IV infusion	—†						
Stelara (ustekinumab) SC injection	✓	✓	✓§	—	✓§	✓§	✓‡§
Taltz (ixekizumab) SC injection	✓	—	✓§	—	✓§	✓§	✓‡§

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Has not yet been evaluated for inclusion on the National Formulary
‡ Prior authorization
§ After failure of Humira
IV = intravenous
NTMB = New-to-Market Block
SC = subcutaneous

Table 10: 2017 Medicare Part D Drug List Availability of Plaque Psoriasis Agents with Optional UM Tools

Product	PDP/ PDP Plus Drug List	Client Drug Lists								
		Select*	Generic Strategy Standard*	Generic Strategy Essential	MMP	Standard†	Expanded	Expanded Performance	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier		4-Tier	5-Tier
Siliq (brodalumab) SC injection	—									
Amjevita (adalimumab-atto) SC injection	—									
Cosentyx (secukinumab) SC injection	—									
Enbrel (etanercept) SC injection	—	—	—	—	—	—	tier 5‡	—	—	—
Erelzi (etanercept-szzs) SC injection	—									
Humira (adalimumab) SC injection	tier 5‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 2‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 4‡§	tier 5‡§
Inflectra (infliximab-dyyb) IV infusion	—									
Otezla (apremilast) oral tablet	—	—	—	—	—	—	tier 5‡	—	—	—
Remicade (infliximab) IV infusion	tier 5‡	tier 5‡	tier 5‡	tier 5‡	tier 2‡	tier 5‡	tier 5‡	tier 5‡	tier 4‡	tier 5‡
Renflexis (infliximab-abda) IV infusion	—									
Stelara (ustekinumab) SC injection	—									
Taltz (ixekizumab) SC injection	—									

* Also available as a Single-Source Generic Strategy drug lists
† Also available as a 1-Tier and 4-Tier drug list
‡ Prior authorization
§ Quantity Limit only on Humira injection 10 mg/0.2 mL, kit 20 mg/0.4 mL, kit 40 mg/0.8 mL, and pen injection 40 mg/0.8 mL
EGWP = Employer Group Waiver Plan
IV = intravenous
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
SC = subcutaneous
UM = utilization management

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Pharmacy &Therapeutics Committee Summary Review

Tremfya® (guselkumab) – Novartis Pharmaceuticals Corporation

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2017

Therapeutic Class: Interleukin-23 inhibitor

FDA Approval Date: 7/13/2017

FDA Indication: Plaque psoriasis

Comparable Products: Taltz (non-preferred), Cosentyx (non-preferred), Stelara (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred

- For initial authorization:
  - Member must be 18 years of age or older; AND
  - Must have a documented negative TB test (i.e. tuberculosis skin test (PPD), an interferon-release assay (IGRA), or a chest x-ray) within 6 months prior to starting therapy; AND
  - Medication must be prescribed by a rheumatologist or dermatologist; AND
  - Member has PP for 6 months or longer; AND
  - Member has PP involves 10% or more of the member's body surface area; AND
  - Member's Psoriasis Area and Severity Index (PASI) score is greater than or equal to 12; AND
  - Member has tried and failed to respond to treatment with at least one of the following:
    - At least 12 weeks of photochemotherapy (i.e. psoralen plus ultraviolet A therapy);
    - At least 12 weeks of phototherapy (i.e. UVB light therapy, Excimer laser treatments) (tanning beds emit mostly UVA light and therefore would not meet this criteria).
    - At least a 4 week trial with topical antipsoriatic agents (i.e. anthralin, calcipotriene, coal tar, corticosteroids, tazarotene); AND
  - Member has tried and failed to respond to treatment of an immunosuppressant (i.e. cyclosporine, methotrexate, acetretin) for at least a 12 week trial; AND
  - Member has tried and failed treatment with both Enbrel and Humira.
  - Dosage allowed: 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter.
- For reauthorization:
  - Must have been retested for TB with a negative result within the past 12 months; AND
  - Member must be in compliance with all other initial criteria; AND
  - Chart notes have been provided that show the member has shown improvement of signs and symptoms of disease; AND
  - Documented member's PASI score improvement.

Clinical Implications/ Place in Therapy:

New drug for Plaque Psoriasis was reviewed. Criteria for Tremfya are written based on trials data from drug's package insert and evidence-based guidelines from American Academy of Dermatology. Criteria aligned with existing drug criteria for Plaque Psoriasis. Non-preferred drug status is recommended.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Tremfya™ (guselkumab) subcutaneous injection Janssen Biotech, Inc

INDICATION

Tremfya (guselkumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy (Tremfya prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Tremfya (guselkumab) was approved by the FDA on July 13, 2017 under a Biologics License Application (BLA) (FDA, 2017a).

DRUG SUMMARY

	Tremfya (guselkumab)
Place in Therapy	• Tremfya serves as an additional biologic therapy for treating moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy. • The American Academy of Dermatology (AAD) 2008 guidelines for the treatment of psoriasis recommend phototherapy, PUVA, methotrexate, oral cyclosporine, oral retinoids (acitretin), and biologic agents for the treatment of moderate-to-severe psoriasis. No specific biologic agents are recommended in the guidelines. • Several biosimilars of TNF-α antagonist have been approved for plaque psoriasis and are expected to be launched in the coming years.
Efficacy	• In two published, phase III, randomized, placebo-controlled, active comparator-controlled trials (N = 837; N =992), Tremfya demonstrated superiority compared with Humira (adalimumab) and placebo in achieving PASI 90 (70% to 73% of Tremfya-treated patients), PASI 75 (86% to 91%), and IGA 0/1 (i.e., skin improvement to "clear" or "almost clear") (84% to 85%) at 16 weeks. • In another active-comparator trial (N = 268), Tremfya demonstrated superiority compared with Stelara (ustekinumab) in achieving IGA 0/1 but not PASI 75 or PASI 90 at 12 weeks. Tremfya was superior to Stelara at 52 weeks in achieving PASI 90.
Safety	• Similar to other biologic therapies in the class, Tremfya has the following warnings & precautions: risk of infection and tuberculosis reactivation • Common adverse events (≥ 1%): upper respiratory infections, headache, injection-site reactions, arthralgia, diarrhea, gastroenteritis, tinea infection, and herpes simplex infection

IGA = Investigator's Global Assessment
PASI = Psoriasis Area and Severity Index
PASI 75 = ≥ 75% reduction of PASI score from baseline
PASI 90 = ≥ 90% reduction of PASI score from baseline
PUVA = psoralen and ultraviolet A light
TNF = tumor necrosis factor

CLINICAL EFFICACY

Table 2: Efficacy of Tremfya (guselkumab) in the Treatment of Moderate to Severe Plaque Psoriasis

Study Evidence level Ib		VOYAGE 1; N = 837 Blauvelt, 2017				VOYAGE 2; N = 992 Reich, 2017			
Study Design		Two published, phase III, multicenter, randomized, double-blind, placebo- and active-controlled trials; patients were randomized to receive Tremfya (guselkumab), Humira (adalimumab), or placebo for 16 weeks in the initial phase.							
		From week 16 to week 48, patients who received placebo were switched to Tremfya for the remaining weeks; patients receiving an active treatment continued current therapy.				From week 16 to week 24, placebo patients were switched to Tremfya, while other treatment arms continued current therapy; at week 28, responders* to therapy were randomized to either Tremfya or a period of withdrawal (i.e., placebo) and retreatment upon loss of ≥ 50% of week-28 PASI† response, while non-responders continued current therapy.			
Inclusion Criteria		Adult patients (mean age 44 years; 70% to 73% male) with moderate to severe plaque psoriasis (IGA‡ score ≥ 3, PASI score ≥ 12, BSA ≥ 10%) for ≥ 6 months; study population at baseline: mean psoriasis duration of 17.5 years, mean BSA involvement of 28%, 75% to 77% had IGA score of 3, mean PASI score of 22, and 21% had prior exposure to biologic agents.							
Exclusion Criteria		Current or history of malignancy, except NMSC, within 5 years; history or symptoms of active tuberculosis; previous exposure to Tremfya or Humira, other TNF inhibitors within 3 months, and treatment targeting interleukins within 6 months from start of clinical trial.							
Treatments		**Tremfya**§ (n = 329)	**Humira**‖ (n = 334)	**Placebo** (n = 174)	**p-value**	**Tremfya**§ (n = 496)	**Humira**‖ (n = 248)	**Placebo** (n = 248)	**p-value**
Results	% of patients with IGA 0/1‡ at week 16**	85.1%	65.9%	6.9%	p < 0.001 vs. placebo¶	84.1%	67.7%	8.5%	p < 0.001 vs. placebo¶
	% of patients with PASI 90 at week 16**	73.3%	49.7%	2.9%		70.0%	46.8%	2.4%	
	% of patients with PASI 75 at week 16	91.2%	73.1%	5.7%		86.3%	68.5%	8.1%	
	% of patients with PASI 75 at week 24	91.2%	72.2%	—	p < 0.001 vs. Humira	89.1%	71.0%	—	p < 0.001 vs. Humira
Safety		In both trials, the most common adverse events (occurring in ≥ 5% of study population) were nasopharyngitis, headache, and upper respiratory tract infections. The safety profiles of Tremfya and Humira were generally similar. In VOYAGE 1, five cases of malignancies were reported in Tremfya-treated patients (e.g., three NMSCs, one prostate cancer, and one breast cancer) vs. one case of NMSC in Humira-treated patients. In VOYAGE 2, two cases of NMSC and one case of prostate cancer were reported with Tremfya vs. no malignances reported with Humira use.							
Comments		More patients in the Tremfya arm achieved clinical responses compared with Humira at week 24 in the VOYAGE 2 trial and at week 48 in the VOYAGE 1 trial (p < 0.001 for both trials). For patients who randomized to the withdrawal group, the median time to a loss of PASI 90 response was 15.2 weeks; IGA and PASI scores were better (p < 0.001) in the maintenance group vs. withdrawal group at 48 weeks.							
Conclusions		Tremfya 100 mg administered subcutaneously was superior to placebo and Humira in achieving PASI 75, PASI 90, and IGA score of 0/1 in patient with moderate-to-severe plaque psoriasis with a generally well-tolerated safety profile that was comparable to Humira.							

* A responder was defined as patient achieving PASI 90
† PASI score ranges from 0 to 72; higher score indicates more severe disease
‡ IGA score for psoriasis ranges from 0 to 5; higher score indicates more severe disease; IGA score of 0/1 means a skin appearance of "clear" or "almost clear"
§ Tremfya (guselkumab) 100 mg subcutaneously at week 0, week 4, week 12, and every 8 weeks through week 44
‖ Humira (adalimumab) 80 mg subcutaneously at week 0 , 40 mg at week 1, and 40 mg every 2 weeks through week 47
¶ P-values vs. Humira (adalimumab) were not reported
** Co-primary endpoint
Evidence level Ib = randomized, controlled trial
BSA = body surface area
IGA = Investigator Global Assessment
NMSC = non-melanoma skin cancer
PASI = Psoriasis Area and Severity Index
PASI 75 = 75% or greater reduction from baseline in PASI score
PASI 90 = 90% or greater reduction from baseline in PASI score
PASI 100 = 100% reduction from baseline in PASI score
TNF = tumor necrosis factor

(Blauvelt, 2017; Reich, 2017)

Reproductive Risk

No data are available on the use of guselkumab in pregnant women to inform the risk of adverse developmental outcomes (Tremfya prescribing information, 2017). Human IgG antibodies are known to cross the placental barrier; therefore, guselkumab may be transmitted from the mother to the developing fetus.

Nursing Mothers

No data are available on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production (Tremfya prescribing information, 2017). While maternal IgG is known to be present in human milk, guselkumab was not detected in animal lactation studies.

Pediatric Use

The safety and efficacy of Tremfya (guselkumab) in pediatric patients have not been established (Tremfya prescribing information, 2017).

Geriatric Use

Of the 1,748 patients who received Tremfya (guselkumab) in clinical trials, 93 patients were 65 years of age or older (Tremfya prescribing information, 2017). Although no overall difference in safety were observed between older and younger patients who received Tremfya (guselkumab), the number of geriatric patients was not sufficient to determine the difference in response to Tremfya (guselkumab) between older and younger patients.

Drug Interactions

No clinically relevant drug interactions have been identified with guselkumab (Tremfya prescribing information, 2017).

Adverse Events

Table 3: Adverse Events Occurring in ≥ 1% of Patients Receiving Tremfya (guselkumab)*

Adverse Event	Tremfya (n = 823)	Humira (adalimumab) (n = 196)	Placebo (n = 422)
Upper respiratory infections	14.3%	10.7%	12.8%
Headache	4.6%	1.0%	3.3%
Injection-site reactions	4.5%	7.7%	2.8%
Arthralgia	2.7%	2.0%	2.1%
Diarrhea	1.6%	1.5%	0.9%
Gastroenteritis	1.3%	2.0%	0.9%
Tinea infection	1.1%	0%	0%
Herpes simplex infection	1.1%	0%	0.5%

* Data through week 16 from VOYAGE 1 and VOYAGE 2 trials
(Tremfya prescribing information, 2017)

Immunogenicity

Approximately 6% of patients treated with Tremfya (guselkumab) developed anti-drug antibodies at up to week 52, and of those, approximately 7% had neutralizing antibodies (Tremfya prescribing information, 2017). About half of the patients with anti-drug antibodies exhibited lower trough levels of guselkumab, including one patient who experienced loss of efficacy after developing high antibody titers. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions.

Determining the severity of disease is a qualitative decision, hinging on measures of disease activity, resistance to prior therapy, and psychosocial considerations (Callen, 2003; Menter, 2011). Mild disease is based on limited BSA involvement, which is generally defined as less than 3% to 5% of BSA (Menter, 2011; National Psoriasis Foundation, 2017a). About 70% to 80% of patients have mild psoriasis that can be controlled using topical therapies alone (Boehncke, 2015). Moderate and severe diseases overlap, and even limited disease may be considered moderate for the purposes of selecting therapy (Callen, 2003; National Psoriasis Foundation, 2017a). Patients with psoriasis of the palms, soles, head and neck, or genitalia, or with more than 5% BSA involvement may be considered to have moderate to severe disease. A summary of therapies for treating plaque psoriasis is listed in Table 4. The AAD guidelines were last updated prior to the approval of Cosentyx (secukinumab), Siliq (brodalumab), Taltz (ixekizumab), Tremfya (guselkumab), and biosimilars of TNF inhibitors.

Table 4: American Academy of Dermatology Recommendations for the Treatment of Plaque Psoriasis

Severity of Psoriasis	Therapies Available*
Limited, localized, or mild	**First-line treatment:** topical agents and/or targeted phototherapy • Corticosteroids: variety of strengths, vehicles, intralesional, tape • Retinoids: tazarotene • Vitamin D derivatives: calcipotriene, calcitriol • Anthralin • Tar preparations • Keratolytic agents: salicylic acid, lactic acid, urea • Lubrication products • Combinations or sequential uses of above agents
Moderate to severe†	• Phototherapy • Photochemotherapy with PUVA • Methotrexate • Cyclosporine (oral) • Oral retinoids: acitretin • Biologic agents: Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), Stelara (ustekinumab) • Combinations of above including topical agents

* Selection of agent depends on the location of the lesion and its severity
† AAD does not recommend one therapy over another
AAD = American Academy of Dermatology
PUVA = psoralen and ultraviolet A light

(Callen, 2003; Menter, 2008; Menter, 2011)

National Institute for Health and Care Excellence (NICE)

NICE guidance recommends Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Otezla (apremilast), Stelara (ustekinumab), or Taltz (ixekizumab) for the treatment of psoriasis (NICE, 2006; NICE, 2008a; NICE, 2008b; NICE, 2009; NICE, 2015; NICE, 2016; NICE, 2017a). Patients are eligible for these therapies if they have failed to respond or are intolerant to standard therapies including cyclosporine, methotrexate, and psoralen and ultraviolet A light (PUVA), and if they have a PASI score $\geq$ 10 and a Dermatology Life Quality Index (DLQI) $\geq$ of 10, except for Remicade (infliximab), which requires the patient to have a PASI $\geq$ 20 and a DLQI $\geq$ 18. Treatment should be discontinued if psoriasis has not shown a measured response after 10 weeks for Remicade (infliximab), 12 weeks for Cosentyx (secukinumab), Enbrel (etanercept), and Taltz (ixekizumab), and 16 weeks for Humira (adalimumab), Otezla (apremilast), and Stelara (ustekinumab).

NICE is expected to publish guidance regarding the use of Tremfya (guselkumab) for the treatment of moderate to severe psoriasis in June 2018 (NICE, 2017b).

FORMULARY CONSIDERATIONS

Tremfya (guselkumab) is a new human IL-23 receptor antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. In two randomized, double-blind, placebo-controlled, and active comparator-controlled trials, Tremfya (guselkumab) demonstrated superiority compared with placebo and Humira (adalimumab) at week 16 in achieving PASI 75, PASI 90, and IGA 0/1 response. Safety concerns associated with Tremfya (guselkumab) include risk of infections (e.g., upper respiratory infections) and TB reactivation. Overall, Tremfya (guselkumab) offers an additional agent for the treatment of moderate to severe plaque psoriasis.

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Pharmacy &Therapeutics Committee Summary Review

Vosevi® (sofosbuvir, velpatasvir, and voxilaprevir) – Gilead Sciences, Inc.

Prepared by: CVS Health / Andrea Enterline and Irina Yaroshenko

Presentation Date: 3/8/2017

Therapeutic Class: Nucleotide analog NS5B polymerase inhibitor, NS5A inhibitor, NS3/4A protease inhibitor

FDA Approval Date: 7/18/2017

FDA Indication: Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection

Comparable Products: Zepatier, Technivie, Viekira, Olysio, Vosevi, Harvoni, Sovaldi, Epclusa

Proposed Designation & Rationale

Recommendation: Non-preferred

- N/A

Clinical Implications/ Place in Therapy:

New drug for Hepatitis C without cirrhosis or with compensated cirrhosis was reviewed. Vosevi's package insert, clinical trials and place on guidelines from American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) was reviewed. Based on other viable options that are currently preferred for treatment it was recommended to place medication in non-preferred category of coverage. It was determined that no policy needed at this time due to variety of other available drug options with existing polices.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir) tablets Gilead Sciences Inc.

INDICATION

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype (GT) 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing a nonstructural protein (NS) 5A inhibitor or who have genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor (Vosevi prescribing information, 2017).

U.S. Food and Drug Administration (FDA)-Review Designation

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) was approved by the FDA on July 18, 2017 with a review designation of 4P (FDA, 2017a). Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is a fixed-dose combination (FDC) tablet of two previously FDA-approved agents and a new molecular entity that underwent priority review and was granted breakthrough therapy designation (FDA, 2017b). An agent may qualify for breakthrough therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2017c).

DRUG SUMMARY

Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	
Place in Therapy	• Vosevi is the first FDA-approved treatment of HCV infection in patients with or without compensated cirrhosis who have GT1, 2, 3, 4, 5, or 6 and have previously been treated with an NS5A inhibitor-containing HCV regimen. Vosevi is also approved for treatment of patients with HCV GT1a and 3 who have been previously treated with a sofosbuvir-containing HCV regimen without an NS5A inhibitor. • Vosevi is an additional treatment option for patients with HCV GT1 who have been previously treated with an NS5A inhibitor and is the first and only FDA-approved agent for patients with chronic HCV infections who have previously received treatment regimens containing an HCV NS5A inhibitor in HCV GT2 through 6. • The 2017 AASLD/IDSA treatment guidelines for HCV recommend Vosevi for patients with GT1, 3, 4, 5, or 6 who have previously failed treatment with an NS5A inhibitor and for patients with GT1a who previously failed a sofosbuvir-containing regimen.
Efficacy	• FDA approval for Vosevi was based on two phase 3 trials demonstrating high rates of SVR12 among patients across all HCV GTs who had been previously treated with a DAA regimen. • In the POLARIS-1 trial, the rate of SVR12 was 96% with Vosevi in patients previously treated with an NS5A inhibitor. • In the POLARIS-4 trial, Vosevi had an SVR12 rate of 98% compared with an SVR rate of 90% with Epclusa (sofosbuvir/velpatasvir) in patients previously treated with a DAA regimen that did not include an NS5A inhibitor.
Safety	• Warnings and precautions: risk of hepatitis B virus reactivation, bradycardia with amiodarone administration • Common AEs (≥ 10%): headache, fatigue, diarrhea, and nausea

AASLD = American Association for the Study of Liver Diseases
AE = adverse event
DAA = direct-acting antiviral
FDA = Food and Drug Administration
GT = genotype
HCV = hepatitis C virus
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
SVR12 = sustained virologic response measured 12 weeks after treatment

Of the 182 DAA-experienced patients who had not received an NS5A inhibitor with Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in the POLARIS-4 trial, one (1%) patient (GT1a) relapsed and qualified for resistance analysis (Vosevi prescribing information, 2017). The NS5A resistance-associated substitution M28T emerged in this patient at relapse. No NS3/4A protease inhibitor (PI) or nucleotide analog NS5B inhibitor substitutions were observed in the patient at relapse.

Effect of Baseline HCV Variants on Treatment Response

Overall, the presence of baseline NS3/4A PI, NS5A inhibitor, and nucleotide analog NS5B polymerase inhibitor resistance-associated substitutions did not alter the SVR rates for DAA-experienced patients in the POLARIS-1 and POLARIS-4 trials who received Vosevi (sofosbuvir/velpatasvir/voxilaprevir) (Vosevi prescribing information, 2017). SVR12 rates in subjects with or without baseline NS3 and NS5A resistance-associated substitutions in the POLARIS-1 and POLARIS-4 trials were all ≥ 97% for patients treated with Vosevi (sofosbuvir/velpatasvir/voxilaprevir).

Cross-Resistance

There exists a possibility of cross-resistance between HCV NS3/4A PIs and HCV NS5A inhibitors by class (Vosevi prescribing information, 2017). Sofosbuvir, velpatasvir, and voxilaprevir were each fully active against substitutions associated with resistance to other classes of DAAs with different mechanism of action (e.g., voxilaprevir was active against virus with NS5A resistance-associated substitutions and nucleotide analog NS5B inhibitor resistance-associated substitutions).

Efficacy and Safety Data in the Elderly

Seventeen percent of patients in the phase III clinical trials for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) were ≥ 65 years of age (Vosevi prescribing information, 2017). Overall, no differences in safety or efficacy were observed between these subjects and younger subjects; however, greater sensitivity of elderly populations cannot be ruled out. There are no dose adjustments of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) recommended in geriatric patients.

SAFETY

Contraindications

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is contraindicated with concomitant rifampin use (Vosevi prescribing information, 2017).

Boxed Warning

RISK OF HEPATITIS B VIRUS (HBV) REACTIVATION IN PATIENTS CO-INFECTED WITH HCV AND HBV

HBV reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV DAAs and were not receiving HBV antiviral therapy (Vosevi prescribing information, 2017). Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in hepatitis B surface antigen (HBsAg) positive patients and in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and hepatitis B core antibody [anti-HBc] positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV DAAs may be increased in these patients. Prior to initiating HCV treatment with Vosevi (sofosbuvir/velpatasvir/voxilaprevir), all patients should be tested for evidence of current or prior HBV infection by measuring HBsAg and ant-HBc. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatic flare or HBV reactivation during HCV treatment with Vosevi (sofosbuvir/velpatasvir/voxilaprevir) and during post-treatment follow-up.

Other Drug Interactions

Velpatasvir and voxilaprevir are inhibitors of drug transporters P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, and OATP1B3; Velpatasvir is also an inhibitor of OATP2B1 (Vosevi prescribing information, 2017). Coadministration of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with BCRP substrates is not recommended. Table 3 describes potentially significant drug interactions with Vosevi (sofosbuvir/velpatasvir/voxilaprevir).

Table 3: Potentially Significant Drug Interactions with Sofosbuvir/Velpatasvir/Voxilaprevir

Interacting Agent	Outcome	Recommendation
Antacids (e.g., aluminum and magnesium hydroxide)	↓ velpatasvir exposure	Separate administration of antacid and sofosbuvir/velpatasvir/voxilaprevir by 4 hours
H_2-receptor antagonists (e.g., famotidine)		Administer H_2-receptor antagonist simultaneously with or staggered from sofosbuvir/velpatasvir/voxilaprevir and doses not to exceed those comparable to famotidine 40 mg twice daily
Proton-pump inhibitors (e.g., omeprazole)		Omeprazole 20 mg may be administered with sofosbuvir/velpatasvir/voxilaprevir. Use with other proton-pump inhibitors has not been studied
amiodarone	Effect on amiodarone, sofosbuvir, velpatasvir, and voxilaprevir concentrations unknown	Coadministration is not recommended; if coadministration is required, cardiac monitoring is recommended
digoxin	↑ digoxin exposure	Therapeutic concentration monitoring of digoxin is recommended
dabigatran	↑ dabigatran	Clinical monitoring of dabigatran is recommended
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir, ↓ velpatasvir, and ↓ voxilaprevir	Coadministration is not recommended
rifampin	↓ sofosbuvir, ↓ velpatasvir, and ↓ voxilaprevir (after multiple doses)	Coadministration with rifampin is contraindicated
rifabutin, rifapentine	↓ sofosbuvir, ↓ velpatasvir, and ↓ voxilaprevir	Coadministration is not recommended
St. John's wort		
atazanavir, lopinavir	↑ voxilaprevir	
tipranavir/ritonavir	↓ sofosbuvir and ↓ velpatasvir	
efavirenz	↓ velpatasvir and ↓ voxilaprevir	
Regimens containing tenofovir disoproxil fumarate	↑ tenofovir	Monitor for tenofovir-associated adverse events
pravastatin	↑ pravastatin	Doses of pravastatin should not exceed 40 mg due to risk of myopathy, including rhabdomyolysis
rosuvastatin	↑ rosuvastatin	Coadministration is not recommended
atorvastatin, fluvastatin, lovastatin, simvastatin	↑ atorvastatin, ↑ fluvastatin, ↑ lovastatin, And ↑ simvastatin	Lowest necessary statin dose based on risk/benefit assessment is recommended
cyclosporine	↑ voxilaprevir	Coadministration is not recommended

H_2 = histamine$_2$

(Vosevi prescribing information, 2017)

HCV is a small, enveloped RNA virus that has been allocated to a unique genus *Hepacivirus* within the family *Flaviridae* (Thomson, 2005). HCV replicates in the cytosol of infected hepatocytes (Soriano, 2005). Similar to other RNA-dependent polymerases, the HCV RNA polymerase (NS5B) generates considerable genetic diversity. On the basis of variations in the nucleotide sequence of HCV, six genotypes (numbered 1 to 6) and more than 50 subtypes (e.g., 1a and 1b) have been identified (CDC, 2017; Khuroo, 2004). HCV genotypes and subtypes are intrinsic characteristics of the transmitted viral strain and do not change during the course of the infection. In the United States, the prevalence of HCV is 1.3% of the general population (Petruzziello, 2016). Approximately 75.2% of patients are infected with HCV GT1, 12.5% with GT2, 10.4% with GT3, and less than 2% with GT4, GT5, or GT6 (Messina, 2014).

The natural history of HCV is quite variable (Wong, 2005). After exposure, 75% to 85% of patients become chronically infected, which is an infection that persists for at least six months (CDC, 2017). HCV is also associated with slowly progressive hepatic fibrosis, with 60% to 70% of patients developing chronic liver disease, 5% to 20% developing cirrhosis over 20 years to 30 years, and 1% to 5% dying from hepatocellular carcinoma (HCC) or cirrhosis. Table 5 illustrates factors that can be associated with a higher risk of fibrosis progression with HCV (AASLD/IDSA, 2017). Approximately 15% to 25% of patients spontaneously clear the infection and do not develop chronic infection (CDC, 2017). The age of infection is linked with risk for chronicity and rate of disease progression, with children and young adults more likely to have spontaneous clearance of the infection and less likely to develop cirrhosis compared with older individuals (Wong, 2005). Although 80% of acute HCV cases are asymptomatic, the most common symptoms include jaundice, fatigue, dark urine, clay-colored stool, abdominal pain, loss of appetite, and nausea (CDC, 2017; WHO, 2017). Most patients who develop chronic HCV will not exhibit any symptoms until liver complications have developed (CDC, 2017).

Table 5: Factors Associated With a Higher Risk of Fibrosis Progression with HCV

Host: Non-Modifiable	Host: Modifiable	Viral
• Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant	• Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance	• Genotype 3 • Coinfection with HBV or HIV

HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus

(AASLD/IDSA, 2017)

In the last few years, treatment for HCV has changed dramatically (Pawlotsky, 2014). The approval of several oral DAAs, including combination products, has revolutionized treatment for HCV. Interferon (IFN)-containing-regimens have largely been replaced by all oral, IFN-free, and ribavirin-free therapies. These newer IFN-free regimens are well tolerated with shorter treatment durations and have cured more than 90% of patients in clinical trials compared with older IFN-based regimens with cure rates between 40% and 45% (Bourliere, 2017; Lam, 2015).

Table 6: AASLD/IDSA Recommended Agents for HCV GT 1a, 1b, 2, 3, 4, 5, and 6*

HCV GT	Medications	Length of Therapy
Patients in whom Previous Treatment with PEG/RBV has Failed		
1a/1b	*No Cirrhosis*	12 weeks
	Zepatier (elbasvir/grazoprevir)†	
	Harvoni (ledipasvir/sofosbuvir)	
	Mavyret (glecaprevir/pibrentasvir)	8 weeks
	Epclusa (sofosbuvir/velpatasvir)	12 weeks
2	**Epclusa**	
	Mavyret	8 weeks
3	**Epclusa**‡	12 weeks
4	**Epclusa**	12 weeks
	Mavyret (I, B)	8 weeks
	Zepatier (IIa, B)	12 weeks
	Harvoni (IIa, B)	
1a/1b	*Compensated Cirrhosis*	
	Zepatier†	
	Mavyret (I, B)	
	Epclusa	
2	**Epclusa**	
	Mavyret (I, B)	
3	**Zepatier + Sovaldi** (I, B)	
	Vosevi (sofosbuvir/velpatasvir/voxilaprevir) (IIb, B)	
4	**Epclusa** (I, A)	
	Zepatier (IIa, B)	
	Mavyret (IIa, B)	
5, 6	*With and Without Cirrhosis*	8 weeks (no cirrhosis)/ 12 weeks (cirrhosis)
	Mavyret (IIa, B)	
	Harvoni (IIa, B)	12 weeks
	Epclusa (IIa, B)	

* Unless otherwise noted, all recommendations depicted are class I, level A (evidence and/or general agreement that a given treatment is beneficial, useful, and effective and data are derived from multiple randomized clinical trials, meta-analyses, or equivalent).
† Patients in whom no baseline NS5A RAVs for elbasvir are detected for HCV-GT1a
‡ Resistance-associated variants testing for Y93H is recommended for cirrhotic patients and RBV should be included in regimen if present
§ For patients with prior NS5A inhibitor failure and cirrhosis, the addition of RBV is recommended (IIa, C)
AASLD = American Association for the Study of Liver Diseases
GT = genotype
HCV = hepatitis C virus
IDSA = Infectious Diseases Society of America
NS = nonstructural protein
PEG = peginterferon
PI = protease inhibitor
RAV = resistance-associated variants
RBV = ribavirin

(AASLD/IDSA, 2017)

Table 7: Comparison of Select FDA-Approved Agents for the Treatment of HCV GT1 through GT6

Agent	Advantages	Disadvantages
All Agents	• All agents have comparable efficacy across GTs and have demonstrated high SVR rates • Allow for IFN-free treatment regimens • All agents are included in the AASLD/IDSA guidelines for HCV and recommendations are similar to the FDA-approved indications	• HBV reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death • Many potential drug interactions
Daklinza (daclatasvir)	• FDA-approved for HCV GT1 or 3 in compensated or decompensated cirrhosis • Recommended treatment regimen for multiple patient populations (e.g., TN or TE, HCV/HIV co-infection, or post-liver transplant) • Recommended by AASLD/IDSA guidelines for use in GT2 or 3 in TN or TE patients with or without cirrhosis or post-liver transplant	• When coadministered with sofosbuvir and amiodarone, serious symptomatic bradycardia may occur
Epclusa (sofosbuvir/velpatasvir)	• Pan-genotypic DAA in compensated or decompensated cirrhosis • One tablet daily with or without food • No dose adjustment required for hepatic impairment • Recommended treatment regimen for multiple patient populations (e.g., TN, TE, HIV/HCV co-infection).	• Use with acid reducing agents may decrease the concentration of velpatasvir • Coadministration with amiodarone may result in serious, symptomatic bradycardia
Harvoni (ledipasvir/ sofosbuvir)	• FDA-approved for HCV GT1, 4, 5, or 6 and in compensated or decompensated cirrhosis • Recommended treatment regimen for multiple patient populations (e.g. TN, TE, HCV/HIV coinfection, post-liver transplant) • Treatment duration may be decreased to 8 weeks in TN GT1 patients without cirrhosis	• Use with acid reducing agents may decrease the concentration of ledipasvir • Coadministration with amiodarone may result in serious, symptomatic bradycardia
Mavyret (glecaprevir/ pibrentasvir)	• Pan-genotypic DAA in patients with or without cirrhosis and in patients with HCV/HIV co-infection or CKD with hemodialysis • Offers 8 week therapy option for TN patients without cirrhosis across all genotypes and for TE patients without cirrhosis with GT1, 2, 4, 5, 6 • FDA-approved for patients with GT1 experienced with an NS5A inhibitor or NS3/4A PI	• Three tablets daily with food • Contraindicated in patients with severe hepatic impairment (Child-Pugh C)

AASLD = American Association for the Study of Liver Diseases
CKD = chronic kidney disease
CYP = cytochrome P450 isoenzyme system
DAA = direct-acting antiviral
ER = extended release
FDA = Food and Drug Administration
GT = genotype
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus
IDSA = Infectious Diseases Society of America
IFN = interferon-alfa
NS = nonstructural protein
OATP = organic anion transporting polypeptides
P-gp = P-glycoprotein
PEG IFN = peginterferon
PI = protease inhibitor
RBV = ribavirin
TE = treatment-experienced
TN = treatment-naive

FORMULARY CONSIDERATIONS

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is the first and only FDA-approved treatment for patients infected with HCV GT 2 through 6 and who have been previously treated with an NS5A inhibitor and is an additional treatment option for patients with HCV GT1 who are treatment experienced with an NS5A inhibitor. In addition, Vosevi (sofosbuvir/velpatasvir/voxilaprevir) serves as another treatment option for patients with HCV GT1a and 3 who previously failed a treatment regimen containing Sovaldi (sofosbuvir). Results from two pivotal clinical trials demonstrated high rates of SVR12 with the administration of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in patients previously treated with DAA regimens, including NS5A inhibitors, with or without cirrhosis across all six major genotypes of HCV. Of note, Vosevi (sofosbuvir/velpatasvir/voxilaprevir) has a warning for a risk of HBV reactivation and serious symptomatic bradycardia when coadministered with amiodarone. The most common adverse events associated with Vosevi (sofosbuvir/velpatasvir/voxilaprevir) include headache, fatigue, diarrhea and nausea. Overall, Vosevi (sofosbuvir/velpatasvir/voxilaprevir) was shown to be safe and efficacious as a pan-genotypic agent for HCV in treatment experienced patients with or without cirrhosis.

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Q1 2018 Therapeutic Class Reviews

Reviewed for P&T Meeting March 22, 2018

Table 1: Therapeutic Classes with **No Recommended Changes**

Therapeutic Classes		P&T Decision
Analgesic Classes Reviewed with No Recommended Changes	Gout	Approved
	Opioid Analgesics	
	Viscosupplements	
	Non-opioid analgesics	
Anti-Infective Classes Reviewed with No Recommended Changes	Antifungals	Approved
	Hepatitis C	
	Influenza Agents	
Endocrine and Metabolic Classes Reviewed with No Recommended Changes	Androgens	Approved
	Injectable Anti-Diabetics	
	Oral Anti-Diabetics	
	Calcium Receptor Antagonists	
	Calcium Regulators	
	Estrogens	
	Glucocorticoids	
	Glucose Elevating Agents	
	Human Growth Hormones	
	Hyperparathyroid Treatment	
	Phenylketonuria Treatment	
	Phosphate Binders	
	Progestins	
	Selective Estrogen Receptor Modulators	
	Thyroid Agents	
	Vasopressin Receptor Antagonists	
	Vasopressins	

Table 2: Therapeutic Classes **with Recommended Changes**

Therapeutic Classes		P&T Decision
N/A	No new clinical literature, new drugs, changes in guidelines, or price updates of Q1 classes since previous review	Approved

NOTE: Class reviews can be found on SharePoint. If you cannot access SharePoint and would like to review the therapeutic class reviews, you may request the class reviews via email.

KY-HUCP0-0944