Drug Monograph

Drug/Drug Class:	**Daklinza™ (daclatasvir dihydrochloride) tablet / Hepatitis C**
Prepared for:	MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Daklinza™ tablets are available in 2 strengths. It is available in a 30 mg tablet and a 60 mg tablet of daclatasvir dihydrochloride respectively. Manufacturer: Bristol-Myers Squibb Company, Princeton, NJ 08543
Summary of Findings:	The combination of Daklinza and sofosbuvir demonstrated efficacy in the treatment of patients with HCV genotype 3 infection in the open-label, single-arm, phase 3 ALLY-3 clinical trial. Treatment-naive patients (n=101) achieved a sustained virological response (SVR) rate (defined as a sustained virological response at post-treatment week 12) of 90% while treatment experienced patients achieved an SVR rate of 86%, for an overall SVR rate of 89%. Patients without cirrhosis achieved a higher SVR rate of 96% than patients with cirrhosis (63%). Post treatment relapse occurred in 9% of treatment-naive and 14% of treatment-experienced patients.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[3]

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with HCV have no symptoms of the disease until liver damage becomes apparent, which may take several years. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections or liver cancer. According to the Centers for Disease Control and Prevention, approximately 2.7 million Americans are infected with HCV of which, approximately 10 percent are genotype 3.

Dosage Form(s) [1]

Daklinza™ tablets are available in 2 strengths. It is available in a 30 mg tablet and a 60 mg tablet of daclatasvir dihydrochloride respectively.

Manufacturer [1]

Bristol-Myers Squibb Company, Princeton, NJ 08543

Indication(s) [1]

Daklinza™ is indicated for the treatment of adult patients with chronic HCV genotype 3 infection, in combination with sofosbuvir.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Daklinza™ is a nonstructural protein 5A (NS5A) inhibitor that interferes with the HCV replication complex via inhibition of viral RNA replication and virion assembly.

Pharmacokinetics:

	Daklinza
Volume of distribution	47 L
Metabolism	Liver, via CYP3A4
Excretion	Feces 88% (53% unchanged) Urine 6.6%% (primarily unchanged)
Half-life	12 to 15 hours
Protein binding	99%

ALLY – 3 Trial

Daklinza plus sofosbuvir treatment for 12 weeks resulted in an overall SVR rate of 89% in patients with genotype 3 HCV infection

STUDY DESIGN	Open-label, phase 3 clinical trial (n=152).
INCLUSION CRITERIA	Treatment-naive (n=101) or treatment-experienced (n=51) patients with chronic HCV genotype 3 infection and HCV RNA levels of at least 10,000 international units/mL.
EXCLUSION CRITERIA	Previous treatment with a NS5A inhibitor, previous discontinuation of sofosbuvir/ribavirin due to intolerance, chronic liver disease not due to HCV, coinfection with HIV or hepatitis B virus, hepatocellular carcinoma, or hepatic decompensation.
TREATMENT REGIMEN	Patients received Daklinza 60 mg orally once daily in combination with sofosbuvir 400 mg orally once daily for 12 weeks.
RESULTS	An overall SVR rate of 89% was achieved, with a 90% rate in treatment-naive patients and an 86% rate in treatment-experienced patients. SVR rates were 96% and 63% in patients without cirrhosis and with cirrhosis, respectively. Of 7 patients who had previously failed sofosbuvir treatment, 5 achieved SVR. Post treatment relapse occurred in 9% of treatment-naive and 14% of treatment-experienced patients.
SAFETY	The combination of Daklinza and sofosbuvir was well-tolerated with no deaths or adverse events that led to discontinuation. Headache, fatigue, and nausea were the most common adverse events..

Contraindications [(1)]

- Concomitant use with strong CYP3A4 inducers (including but not limited to carbamazepine, phenytoin, rifampin, St John's wort)

Warnings and Precautions [(1)]

- Concomitant use of amiodarone with sofosbuvir in combination with direct-acting HCV antivirals, including daclatasvir; cardiac arrest and serious bradycardia including cases requiring pacemaker intervention have been reported; concomitant use not recommended; monitoring recommended (including initial inpatient monitoring) if concomitant use cannot be avoided or if amiodarone was discontinued just prior to HCV treatment.
- Concomitant use with dabigatran etexilate; not recommended in certain renal impairment groups.
- Concomitant use with digoxin; monitoring and dose reductions of digoxin may be required.
- Concomitant use with strong CYP3A inhibitors or moderate CYP3A inducers; dosage adjustments recommended

Adverse Effects [1]

Most Common, ≥ 5%	Daklinza/Sofosbuvir (n=152)
Headache	14%
Fatigue	14%
Nausea	8%
Diarrhea	5%

Drug Interactions [1]

- Amiodarone
- CYP3A inducers, moderate or strong: carbamazepine, dexamethasone, efavirenz, bosentan, phenytoin, rifampin, rifabutin, St. John's wort
- CYP3A inhibitors, moderate or strong: erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole, indinavir, atazanavir, voriconazole
- Dabigatran etexilate
- Digoxin
- Lipid-lowering agents: atorvastatin, rosuvastatin, simvastatin, fluvastatin

Dosage and Administration [1]

The recommended dosage is 60 mg orally once daily, with or without food, in combination with sofosbuvir for 12 weeks; the optimum duration in patients with cirrhosis has not been determined. Dosage adjustments are recommended with concomitant strong CYP3A inhibitors or moderate CYP3A inducers.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Daclatasvir	Daklinza	Bristol-Myers Squibb	30 mg tablets	1 tablet daily	$22,725
			60 mg tablets	1 tablet daily	$22,725
Sofosbuvir	Sovaldi	Gilead Sciences	400 mg tablets	1 tablet daily	$30,300

* Maximum Allowable Cost

Conclusion

Daklinza™ is an orally administered direct-acting antiviral agent that is indicated in combination with sofosbuvir for the treatment of chronic HCV genotype 3 infection. The combination of

Daklinza and sofosbuvir is an all-oral regimen that provides an effective option for treatment without the use of interferon or ribavirin. In the open-label, single-arm, phase 3 ALLY-3 clinical trial, treatment-naive patients (n=101) achieved an SVR rate of 90%, while treatment experienced patients achieved an SVR rate of 86% after a 12-week course of Daklinza and sofosbuvir. SVR rates were reduced in patients with cirrhosis compared with patients without cirrhosis (63% vs 96%) and the optimum duration of therapy for cirrhotic patients has not been established. A significant potential for serious drug interactions warrants close monitoring when concomitant drugs are given with Daklinza and sofosbuvir, particularly amiodarone, CYP3A inhibitors, and CYP3A inducers. The combination of Dacklinza and sofosbuvir was well tolerated in the ALLY-3 trial, with no deaths or adverse events that led to discontinuation. Headache, fatigue, and nausea were the most common adverse events. Safety and efficacy in liver transplant patients or those with decompensated cirrhosis have not been established.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Daklinza™, daclatasvir tablets. Bristol-Myers Squibb Company, Princeton, NJ, 07/2015.
2. Nelson DR, Cooper JN, Lalezari JP et al: All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015; 61(4):1127-1135.
3. FDA approves new treatment for chronic hepatitis C genotype 3 infections. Retrieved 11/25/2015 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455888.htm

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