PDL NEW DRUG REVIEW

Proprietary Name: Daklinza®
Common Name: daclatasvir dihydrochloride
PDL Category: Hepatitis C Agents

Comparable Products	Preferred Drug List Status
Pegasys	Preferred
Ribavirin	Preferred

Summary

Indications and Usage: For use with sofosbuvir for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infections. Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving Daklinza® in combination with sofosbuvir for 12 weeks.

There is no pregnancy category for this medication; however, the risk summary indicates that there is no information available to inform a drug-associated risk in pregnant women. It is recommended that the benefits and risks of therapy be considered prior to using Daklinza® in pregnancy. The safety and efficacy of use in children younger than 18 years have not been established.

Dosage Forms: Biconvex tablets: 30mg daclatasvir (equivalent to 33mg daclatasvir dihydrochloride), 60mg daclatasvir (equivalent to 66mg daclatasvir dihydrochloride)

Recommended Dosage: Take 60mg PO QD in combination with sofosbuvir for 12 weeks. The optimal duration of use for patients with cirrhosis has not been established. If taken concomitantly with strong CYP3A inhibitors (such as atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, or voriconazole), it is recommended to reduce the dose of Daklinza® to 30mg QD. If taken concomitantly with moderate CYP3A inducers (such as bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, rifapentine), it is recommended to increase the dose of Daklinza® to 90mg QD.

If sofosbuvir is permanently discontinued in a patient taking Daklinza®, then Daklinza® should also be discontinued.

Dose adjustments are not required for patients with renal impairment or for patients with mild to severe hepatic impairment. The safety and efficacy of use in patients with decompensated cirrhosis or in liver transplant patients have not been established.

Drug Interactions: Use of Daklinza® is not recommended with dabigatran in specific renal impairment groups. Co-administration of amiodarone with Daklinza®/sofosbuvir is not recommended. Digoxin levels should be monitored and dose adjustments should be made as needed if used concomitantly with Daklinza®. It is recommended to monitor for HMG-CoA reductase inhibitor associated adverse events, such as myopathy if used concomitantly with Daklinza®. It is recommended to monitor for Daklinza® adverse events if used concomitantly with moderate CYP3A

inhibitors (such as atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, or verapamil). In addition, refer to the contraindications section and recommended dosage adjustment section for other DDIs.

Common Adverse Drug Reactions: *There was no placebo data, thus the listed % incidence for adverse drug reactions= reported % incidence for drug (Daklinza® plus sofosbuvir).* The most frequently reported adverse events included headache (14%), fatigue (14%), nausea (8%), and diarrhea (5%). Transient lipase elevations >3 times the upper limit of normal (ULN) were seen in 2%.

There have been postmarketing reports of cases of symptomatic bradycardia and cases requiring pacemaker intervention when amiodarone is coadministered with sofosbuvir in combination with another HCV direct-acting antiviral, including Daklinza®. The concomitant use of amiodarone with Daklinza®/sofosbuvir is not recommended; however, for patients taking amiodarone who have no alternative treatment options, it is recommended to counsel patients about the risk of serious symptomatic bradycardia. Furthermore, cardiac monitoring in an outpatient setting for the first 48 hours of co-administration is recommended.

Contraindications: In combination with drugs that strongly induce CYP3A, including but not limited to include anticonvulsants (phenytoin, carbamazepine), antimycobacterial agents (rifampin), and herbal products (St. John's wort). Note that this list is not a comprehensive list of all drugs that strongly induce CYP3A.

Manufacturer: Bristol-Myers Squibb

Analysis: Daclatasvir, the active ingredient of Daklinza®, is a direct-acting antiviral agent (DAA) against the hepatitis C virus. It is an inhibitor of HCV non-structural protein 5A (NS5A); it binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly.

One 12-week, open-label, phase 3 study (ALLY-3) was performed to assess the safety and efficacy of Daklinza® in combination with sofosbuvir, and included patients with chronic HCV genotype 3 infection and compensated liver disease who were either treatment naïve (N=101) or treatment-experienced (N=51). Most treatment-experienced patients had failed prior treatment with peginterferon/ribavirin. Sustained virologic response (SVR) was the primary endpoint and results are illustrated in the table below.

Treatment Outcomes	Treatment-Naïve (N=101)	Treatment-Experienced (N=51)	Total (N=152)
SVR All	90%	86%	89%
SVR No cirrhosis	98%	92%	96%
SVR with cirrhosis	58%	69%	63%
Outcomes for subjects without SVR			
On-treatment virologic failure	1%	0%	0.7%
Relapse	9%	14%	11%

Place in Therapy: Daklinza® is the first product FDA approved for genotype 3 HCV infection to be used in combination with sofosbuvir without the need for concomitant use with interferon or ribavirin. Significant drug interactions need to be monitored for as daclatasvir is a substrate of CYP3A and an inhibitor of P-glycoprotein (P-gp) transporters. Some drug interactions require dose adjustments of Daklinza®, and numerous drugs are contraindicated for concomitant use. The evidence-based IDSA/AASLD guidelines have been updated to include Daklinza® and list it as a potential treatment for genotypes 1 and 2 in addition to the FDA label approval for genotype 3. This is a dynamic, rapidly changing therapeutic area and the recommendation for treatment for specific genotypes and clinical situations are continuing to evolve.

Daklinza® should remain non-preferred and require clinical prior authorization to verify diagnosis, concomitant use of sofosbuvir, and to monitor for drug interactions.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**
- ☐ **Preferred with Conditions**

References

[1] Daklinza [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.

[2] FDA News Release: FDA approves new treatment for chronic hepatitis C genotype 3 infections. Website: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455888.htm. Accessed August 2015.

[3] American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. (2015) Recommendations for Testing, Managing, and Treating Hepatitis C. Available at http://www.hcvguidelines.org/sites/default/files/full_report.pdf Accessed August 2015.