DACLATASVIR

Generic	Brand	HICL	GCN	Exception/Other
DACLATASVIR DIHYDROCHLORIDE	DAKLINZA	41377		

***********Customer Service/PAC Alert************
(For Internal Use Only)

THIS IS A HIGH-IMPACT MEDICATION. DO NOT OVERRIDE OR APPROVE WITHOUT SUBMITTING FOR PHARMACIST REVIEW.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of hepatitis C, genotype 1 or genotype 3 infection and meet **ALL** of the following criteria?
   - Patient at least 18 years of age
   - Patient currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (e.g., a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
   - Evidence of current HCV infection and chronic HCV infection documented by at least **ONE** detectable HCV RNA level within the past 6 months
   - Patient is 1) without cirrhosis or 2) has decompensated cirrhosis or 3) post-liver transplant patient (with or without cirrhosis)
   - The request is for Daklinza is in combination with Sovaldi

   CLINICAL PHARMACIST: Patient must also meet all criteria in Sovaldi guideline to be approvable for both agents. Review hepatitis C MRF and Sovaldi request to ensure patient meets criteria for both agents.

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

2. Does the patient meet at least **ONE** of the following criteria?
   - Patient has a limited life expectancy (less than 12 months) due to non-liver related comorbid conditions (e.g., physician attestation)
   - Patient is concurrently taking the following medications:
     - For Daklinza: amiodarone, carbamazepine, phenytoin, or rifampin **OR**
     - For Sovaldi: phenobarbital, oxcarbazepine, rifabutin, rifapentine, or tipranavir/ritonavir

   If yes, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.
   If no, continue to #3.

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GUIDELINES FOR USE (CONTINUED)

3. Does the patient meet **ONE** of the following diagnoses?
   - Decompensated cirrhosis (moderate or severe hepatitis impairment (Child-Pugh B or C))
   - Status post-liver transplant (with or without cirrhosis)

   If yes, continue to #4.
   If no, continue to #6.

4. Is the request for triple therapy using Daklinza/Sovaldi and ribavirin?

   If yes, continue to #5.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

5. Does the patient meet **ONE** of the following criteria for the patient type? [**NOTE:** An individual who has completed a full course of therapy with Mavyret, Harvoni or Epclusa that did not achieve SVR will not be approved]
   - Genotype 1, decompensated cirrhosis: short trial of Harvoni or Epclusa OR contraindication to Harvoni and Epclusa
   - Genotype 1, post-liver transplant: short trial of Harvoni or Mavyret OR contraindication to Harvoni and Mavyret
   - Genotype 3, decompensated cirrhosis short trial of or contraindication to Epclusa
   - Genotype 3, post-liver transplant WITHOUT cirrhosis: short trial of or contraindication to Mavyret
   - Genotype 3, post-liver transplant with compensated cirrhosis: short trial of Epclusa or Mavyret OR contraindication to Epclusa and Mavyret

   If yes, continue to #7.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

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GUIDELINES FOR USE (CONTINUED)

6. Does the patient meet **ONE** of the following criteria? [**NOTE:** An individual who has completed a full course of therapy with Mavyret, Harvoni or Epclusa that did not achieve SVR will not be approved]
   - Genotype 1, without cirrhosis: treatment naïve or treatment experienced with a peginterferon and ribavirin regimen AND a short trial of Epclusa, Harvoni or Mavyret OR a contraindication Epclusa, Harvoni and Mavyret
   - Genotype 3, without cirrhosis: treatment naïve or treatment experienced with a peginterferon and ribavirin regimen AND a short trial of Epclusa or Mavyret OR a contraindication to Epclusa and Mavyret

   If yes, continue to #7.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

7. Is the patient using any of the following moderate CYP3A inducers while taking Daklinza in combination with Sovaldi: rifapentine, bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, or nevirapine?
   CLINICAL PHARMACIST: Patient is on combination therapy with Sovaldi; please also review Sovaldi prior authorization guideline, member history, and hepatitis C MRF, if available to ensure appropriate length of approval and that the patient also meets approval for Sovaldi.

   If yes, **approve Daklinza 90mg strength for 12 weeks by GPID with a quantity limit of #1 tablet per day. (NOTE: 90mg tablet used for drug interactions listed above)**
   APPROVAL TEXT: Prior authorization is approved for a 12-week combination regimen with Daklinza and Sovaldi.

   If no, continue to #8.

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GUIDELINES FOR USE (CONTINUED)

8. Is the patient concurrently using any of the following with Daklinza?
   - HIV protease inhibitors (atazanavir with ritonavir, indinavir, nelfinavir, saquinavir)
   - A cobicistat-containing regimen (exception: darunavir/cobicistat does not require Daklinza 30mg dose), such as atazanavir/cobicistat, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, or other cobicistat-containing regimen
   - Strong CYP3A inhibitors, such as clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, or voriconazole

   If yes, **approve Daklinza 30mg strength for 12 weeks by GPID with a quantity limit of #1 tablet per day. (NOTE: 30mg tablet used for drug interactions listed above)**
   APPROVAL TEXT: Prior authorization is approved for a 12-week combination regimen with Daklinza and Sovaldi.

   If no, **approve Daklinza 60mg strength for 12 weeks by GPID with a quantity limit of #1 tablet per day.**
   APPROVAL TEXT: Prior authorization is approved for a 12-week combination regimen with Daklinza and Sovaldi.

DENIAL TEXT: The guideline named **DACLATASVIR (Daklinza)** requires a diagnosis of hepatitis C genotype 1 or genotype 3 infection. **ALL** the following criteria must be met:
- Age at least 18 years old
- Currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (e.g., a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
- Evidence of current HCV infection and chronic HCV infection as documented by at least ONE detectable HCV RNA level within past 6 months
- Must be taking Daklinza in combination with Sovaldi, and must meet all required criteria for Sovaldi

The medication will not be approved for ANY of the following:
- Patient is concurrently using any of the following with Daklinza: amiodarone, carbamazepine, phenytoin, or rifampin
- Patient is concurrently using any of the following medications with Sovaldi: phenobarbital, oxcarbazepine, rifabutin, rifapentine, or tipranavir/ritonavir
- Patient has a limited life expectancy (less than 12 months) due to non-liver related comorbid conditions
- *Patients with compensated cirrhosis (Child-Pugh A) that are not status post liver transplant*

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GUIDELINES FOR USE (CONTINUED)

In addition, the following criteria must also be met:
For genotype 1 infection:

- Patients without cirrhosis:
  - Patients must be treatment naïve or treatment experienced with previous trial of peginterferon and ribavirin **AND**
  - Previous trial of Epclusa, Harvoni or Mavyret required (e.g., adverse effect, intolerance early in therapy) or contraindication to Epclusa, Harvoni and Mavyret; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
- Patients with decompensated cirrhosis:
  - Previous trial of Epclusa or Harvoni required (e.g., adverse effect, intolerance early in therapy), or contraindication to Epclusa and Harvoni; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
  - Concurrent ribavirin use required
- Patients post-liver transplant:
  - Previous trial of Harvoni or Mavyret required (e.g., adverse effect, intolerance early in therapy, or contraindication to Harvoni and Mavyret; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
  - Concurrent ribavirin use required

For genotype 3 infection:

- Patients without cirrhosis:
  - Patients must be treatment naïve or treatment experienced with previous trial of peginterferon and ribavirin **AND**
  - Previous trial of Epclusa or Mavyret required (e.g., adverse effect, intolerance early in therapy), or contraindication to Epclusa and Mavyret; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
- Patients with decompensated cirrhosis:
  - Previous trial of Epclusa required (e.g., adverse effect, intolerance early in therapy, or contraindication to therapy; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
  - Concurrent ribavirin use required
- Post-liver transplant, without cirrhosis:
  - Previous trial of Mavyret required (e.g., adverse effect, intolerance early in therapy), or contraindication to therapy; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
  - Concurrent ribavirin use required
- Post-liver transplant, with compensated cirrhosis
  - Previous trial of Epclusa or Mavyret required (e.g., adverse effect, intolerance early in therapy) or contraindication to Epclusa and Mavyret; [an individual who has completed a full course of therapy that did not achieve SVR will not be approved]
  - Concurrent ribavirin use required

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RATIONALE
Ensure appropriate utilization of Daklinza (daclatasvir).

FDA APPROVED INDICATIONS
For use with Sovaldi (sofosbuvir), with or without ribavirin, for the treatment of chronic hepatitis C genotype 1 and 3 infections in adults.

Limitations of Use:
- Sustained virologic response (SVR) rates are reduced in genotype 3 patients with cirrhosis receiving Daklinza in combination with Sovaldi for 12 weeks.

FDA APPROVED DOSAGE
One 60mg tablet taken once daily in combination with Sovaldi (sofosbuvir). Reduce Daklinza dosage to 30mg once daily with strong CYP3A inhibitors and increase dosage to 90mg once daily with moderate CYP3A inducers.

FDA APPROVED DOSAGE
Recommended treatment regimen and duration for Daklinza in patients with genotype 1 or 3 HCV:

Genotype 1	Patients without cirrhosis	Daklinza + Sovaldi for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated cirrhosis (Child-Pugh B or C)	Daklinza + Sovaldi + ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	Daklinza + Sovaldi for 12 weeks
	Compensated (Child-Pugh A) or decompensated (Child Pugh B or C) cirrhosis; or post liver transplant	Daklinza + Sovaldi + ribavirin for 12 weeks

OTHER INFORMATION
EFFICACY
The efficacy of Daklinza for treatment of hepatitis C genotype 3 was studied in the phase 3 ALLY-3 trial, an open-label trial with 152 participants with chronic hepatitis C genotype 3 infection and compensated liver disease. Participants received Daklinza 60mg plus sofosbuvir for 12 weeks. The primary efficacy endpoint was SVR; SVR was defined as HCV RNA levels below the lower limit of quantification at post-treatment week 12 (SVR12). Of the participants, 66% (n=101) were treatment naïve and 34% (n=51) were treatment experienced. The majority of treatment-experienced patients had failed a prior regimen of peginterferon plus ribavirin, but 14% (7 subjects) had previously received a sofosbuvir regimen. Other patient characteristics in the ALLY-3 trial included the following: mean age 55 years (range 24-73 years), 21% with compensated cirrhosis, 59% male, 90% white, 5% Asian, and 4% of African descent. The majority of patients (76%) had baseline HCV RNA levels greater than or equal to 800,000 IU/mL.

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FDA APPROVED INDICATIONS (CONTINUED)

OTHER INFORMATION
EFFICACY
Table 1- Treatment results of the ALLY-3 trial: Daklinza in combination with Sovaldi for treatment of hepatitis C genotype 3 (*From Daklinza prescribing information*)

Treatment Outcomes	Treatment-Naive n=101	Treatment-Experienced n=51	Total n=152
SVR			
All	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis[a]	98% (80/82)	92% (35/38)	96% (115/120)
With cirrhosis	58% (11/19)	69% (9/13)	63% (20/32)
Outcomes for subjects without SVR			
On-treatment virologic failure[b]	1% (1/101)	0	0.7% (1/152)
Relapse[c]	9% (9/100)	14% (7/51)	11% (16/151)

[a] Includes 11 subjects with missing or inconclusive cirrhosis status.
[b] One subject had quantifiable HCV RNA at end of treatment.
[c] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at the end of treatment.

Additional ALLY clinical trials are underway to study the Daklinza/Sovaldi combination for hepatitis C genotypes 1-6, in patients with cirrhotic and post-liver transplant patients, as well as those with HIV coinfection. However, the current prescribing information states that SVR rates are reduced in patients with cirrhosis, and the optimal duration of Daklinza and Sovaldi for patients with cirrhosis has not been established.

SAFETY
Common adverse effects of Daklinza (reported in 10% or more of participants in clinical trials) include headache and fatigue.

Daklinza is contraindicated for patients concurrently using medications that are strong inducers of CYP3A4, including phenytoin, carbamazepine, rifampin and St. John's Wort. Using Daklinza in combination with strong CYP3A4 inducers may lead to loss of virologic response with Daklinza.

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FDA APPROVED INDICATIONS (CONTINUED)

SAFETY
Caution should be used with concurrent use of CYP3A inhibitors or CYP3A inducers. Patients using strong CYP3A inhibitors (e.g., atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, or voriconazole) will require a dosage decrease to Daklinza 30mg daily. Patients using concurrent moderate CYP3A inducers (e.g., bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, or rifapentine) will require a dosage increase to Daklinza 90mg daily.

Daklinza should not be administered concurrently with amiodarone for patients using the Daklinza/Sovaldi regimen. Serious and symptomatic bradycardia may result for individuals on amiodarone using Sovaldi with any other direct acting HCV antiviral, including Daklinza. The risk of bradycardia due to this drug interaction increases for patients using beta blockers, those with underlying cardiac comorbidities, or those with advanced liver disease. Cardiac monitoring can be considered for patients with no alternative treatment options that require this combination plus amiodarone.

Use of Daklinza in patients on digoxin will require digoxin dosage reduction (usually 30-50%) during Daklinza. Monitor serum digoxin concentrations before starting Daklinza.

Daklinza increases dabigatran serum concentrations, and could lead to increased risk of bleeding in certain populations. Patients with reduced renal function using dabigatran should use caution and avoid concurrent use of Daklinza when possible.

No dosage adjustment of Daklinza is required for patients with any degree of renal impairment. No dosage adjustment of Daklinza is required for patients with mild, moderate, or severe hepatic impairment. The safety and efficacy of Daklinza in patients with decompensated cirrhosis has not been established.

Daklinza has not been studied in human pregnancy and lactation studies. Animal studies show no evidence of fetal harm at exposures of 6-22 times the recommended human dose of Daklinza 60mg, but embryofetal toxicity occurred at doses of 33-98 times the recommended human dose. Animal studies showed daclatasvir is present in the milk of lactating rats.

Cross-resistance is expected for Daklinza and other NS5A inhibitors. Cross-resistance for other classes of direct-acting antivirals is not expected. The efficacy of Daklinza/Sovaldi has not been studied in patients who have previously failed treatment with regimens that include an NS5A inhibitor.

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REFERENCES

- Daklinza [Prescribing Information]. Princeton, NJ: Bristol Myers Squibb; February 2017.
- Guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) Recommendations for Testing, Managing, and Treating hepatitis C. Available online at http://www.hcvguidelines.org/full-report-view Accessed July 26, 2016.

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 01/01/18
Created: 08/15
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P&T Approval: 10/17