This drug requires a written request for prior authorization. All requests for hepatitis C medications require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

1. Does the patient have one or more of the following conditions?
   - A limited life expectancy (less than 12 months) due to non-liver related comorbid conditions (e.g., physician attestation)
   - Concurrent use with any of these (contraindicated or not recommended by the manufacturer, or agents that require Daklinza 90mg dosage) medications: amiodarone, carbamazepine, phenytoin, rifampin, rifapentine, bosentan, dexamethasone, modafinil, or nafcillin

   If yes, do not approve.
   **DENIAL TEXT**: See the denial text at the end of the guideline.

   If no, continue to #2.

2. Does the patient meet the following criteria?
   - patient at least 18 years of age
   - hepatitis C, genotype 3
   - patient currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model

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

3. Does the patient have a recent HCV infection documented by two detectable HCV RNA levels separated by 6 months (with one level within the last 6 months) OR does the patient have chronic HCV (prior to the last 6 months) supported by a past diagnosis of hepatic C documented with chart notes of HCV-related biopsies, RNA levels, history of diagnosis, other HCV lab work, or HCV prescriptions and the patient has one detectable HCV RNA level within the last 6 months?

   If yes, continue to #4.
   If no, do not approve.
   **DENIAL TEXT**: See the denial text at the end of the guideline.

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DACLATASVIR

GUIDELINES FOR USE (CONTINUED)

4. Does the patient have cirrhosis?
   
   If yes, do not approve.
   **DENIAL TEXT:** See the denial text at the end of the guideline.
   If no, continue to #5.

5. Does the patient have evidence of fibrosis stage 3 as determined by any **ONE** of the following?
   - Metavir score F3 from liver biopsy
   - APRI score of 1.5 to 2.0
   - Fibroscan score of 9.5kPa to 12.5kPa
   - Fibrotest result of 0.58 to 0.74

   If yes, continue to #7.
   If no, continue to #6.

6. Does the patient have Metavir Stage 2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, porphyria cutanea tarda, diabetes type 2, hepatitis B, or HIV coinfection? **Note:** Metavir Stage 2 can be determined by any one of the following:
   - Metavir score F2 from liver biopsy
   - APRI score of 0.78 to 1.49
   - Fibroscan score of 7.65kPa to 9.49kPa
   - Fibrotest result of 0.50 to 0.57

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

7. Has the patient been evaluated to be absent of current alcohol and other substance abuse, with 1) validated screening instruments (e.g., AUDIT or AUDIT C) or via physician attestation **AND** 2) a urine toxicology screen at baseline?

   If yes, continue to #8.
   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)

8. Has the patient had a previous trial of Sovaldi triple therapy (Sovaldi/peginterferon/ribavirin) for 12 weeks?
   
   If yes, continue to #10.
   If no, continue to #9.

9. Does the patient have a contraindication to interferon (for example, concurrent diagnosis of autoimmune hepatitis or other autoimmune disorder; a known hypersensitivity reaction such as urticaria, angioedema, bronchoconstriction and anaphylaxis to alpha interferons, PEG, or any component of peginterferon; documented depression; decompensated hepatic disease; a baseline neutrophil count below 1,500 per microliter, a baseline platelet count below 90,000, or a baseline hemoglobin below 10g/dL that has not responded to treatment)?

   If yes, continue to #10.
   If no, do not approve.

   DENIAL TEXT: See the denial text at the end of the guideline.

10. Has the patient received prior treatment (e.g., treatment-experienced patient) for hepatitis C with Harvoni (ledipasvir/sofosbuvir)?

    If yes, do not approve.
    DENIAL TEXT: See the denial text at the end of the guideline.
    If no, continue to #11.

11. Is the patient using Daklinza in combination with Sovaldi (sofosbuvir)?

    If yes, continue to #12.
    If no, do not approve.

    DENIAL TEXT: See the denial text at the end of the guideline.

12. Is the patient using a medication that contains efavirenz (Atripla or Sustiva) or etravirine (Intelex) while taking Daklinza in combination with Sovaldi (sofosbuvir)?

    If yes, approve for 12 weeks by HICL for #2 tablets per day.
    If no, approve for 12 weeks by HICL for #1 tablet per day.

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DACLATASVIR

GUIDELINES FOR USE (CONTINUED)

INITIAL DENIAL TEXT: Our guideline for DACLATASVIR requires a diagnosis of hepatitis C. In addition, the patient must meet ALL of the following criteria:

- Genotype 3 hepatitis C
- Age at least 18 years old
- Currently supervised by a gastroenterologist, infectious disease specialist, physician specializing in the treatment of hepatitis (for example, a hepatologist), or a specially trained group such as ECHO (Extension for Community Healthcare Outcomes) model
- Evidence of fibrosis stage 3 (Metavir F3 equivalent) or Metavir F2 with another condition listed as “high priority” or “highest priority” for treatment, such as liver transplant recipient, severe extra-hepatic hepatitis C, other co-existing liver disease such as non-alcoholic steatohepatitis, debilitating fatigue, or porphyria cutanea tarda, diabetes type 2, hepatitis B or HIV coinfection
- Documentation of recent HCV infection (e.g., with at least two detectable HCV RNA levels separated by 6 months) OR documentation of chronic hepatitis C (e.g., chart notes of biopsies, RNA levels, history of diagnosis, other HCV lab work, and/or previous HCV prescriptions) with at least one detectable HCV RNA level.
- Must be taking Daklinza in combination with Sovaldi
- Patient must be evaluated for (and absent of) current alcohol and other substance abuse with validated screening instruments (e.g., AUDIT or AUDIT C) or physician attestation AND a urine toxicology screen at baseline
- Previous trial of Sovaldi/peginterferon/ribavirin triple therapy regimen, unless patient meets ONE of the following criteria below for interferon ineligibility:
  - Concurrent diagnosis of autoimmune hepatitis or other autoimmune disorder
  - A known hypersensitivity reaction such as urticaria, angioedema, bronchoconstriction and anaphylaxis to alpha interferons, PEG, or any component of peginterferon
  - Documented depression
  - Decompensated hepatic disease
  - Baseline neutrophil count below 1,500 per microliter
  - Baseline platelet count below 90,000
  - Baseline hemoglobin below 10g/dL that has not responded to treatment)

Daklinza will not be approved for the following patients:

- Patient using any of the following medications concurrently while on Daklinza: amiodarone, carbamazepine, phenytoin, rifampin, rifapentine, bosentan, dexamethasone, modafinil, or nafcillin
- Patients with cirrhosis
- Patients with previous trial of Harvoni
- Patients with limited life expectancy (less than 12 months) due to non-liver related comorbid conditions.

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DACLATASVIR

RATIONALE
Ensure appropriate utilization of Daklinza (daclatasvir).

FDA APPROVED INDICATIONS
For the treatment of chronic hepatitis C genotype 3 infection in adults.

Limitations of Use:
- Sustained virologic response (SVR) rates are reduced in patients with cirrhosis.

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

For genotype 3, duration of therapy is as follows:

<table>
<thead>
<tr>
<th>Treatment naïve or treatment experienced, without cirrhosis</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with cirrhosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimal duration of treatment has not been determined</td>
</tr>
</tbody>
</table>

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.
OTHER INFORMATION (CONTINUED)
EFFICACY (CONTINUED)
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)

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

\(^a\) 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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DACLATASVIR

SAFETY (CONTINUED)
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 inhibitors (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

- 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

<table>
<thead>
<tr>
<th>Library</th>
<th>Commercial</th>
<th>NSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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