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APPLICATION NUMBER:

206843Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley MD MPH
Subject	Deputy Office Director Decisional Memo
NDA #	206843
Applicant Name	Bristol Myers Squibb
Date of Submission	February 13, 2015
PDUFA Goal Date	August 13, 2015
Proprietary Name / Established (USAN) Name	Daklinza/ daclatasvir
Dosage Forms / Strength	30 and 60 mg tablets
Proposed Indication	For use with sofosbuvir for the treatment of adults with chronic hepatitis C genotype 3 infection
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Wendy Carter DO
Statistical Review	Wen Zang PhD.
Pharmacology Toxicology Review	L. Peyton Myers PhD
Product Quality Reviews	ChunChun Zhang PhD, Sandra Suarez Sharp PhD, Bryan Riley PhD
Virology Review	Patrick Harrington PhD, Eric Donaldson PhD, Lalji Mishra PhD
Clinical Pharmacology Review	Stanley Au PharmD BCPS, Fang Li, PhD
CDTL Review	Kimberly Struble, PharmD
Div. Director Review	Debra Birnkrant, MD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1. Introduction

Daclatasvir (DCV) is a new molecular entity NS5A replication inhibitor submitted for the proposed indication of treatment of chronic hepatitis C virus (HCV) genotype 3 infection. The dosage form is a tablet in strengths of 30 mg and 60 mg. The proposed adult dosage is 60 mg once daily (with dose adjustments to 30 mg or 90 mg once daily when co-administered with certain interacting drugs).

NDA 206843 for DCV was originally submitted by the applicant on March 31, 2014 with NDA 206844 for asunaprevir (ASV) as the two products had been studied together in clinical trials. The original NDA sought to provide evidence of efficacy for the treatment of HCV genotypes (b) (4) with the combination of DCV and ASV. A hepatotoxicity signal was seen in clinical trials with the combination of DCV and ASV, particularly in Japanese subjects. On October 6, 2014, the applicant withdrew NDA 206844 for ASV. As NDA 206844 was withdrawn, NDA 206843 did not contain sufficient evidence of the safety and efficacy of DCV without ASV for the treatment of HCV. A Complete Response Letter was issued on November 25, 2014 stating that before the application can be approved, clinical data to support the safety and efficacy of DCV in combination with other antiviral agents for the treatment of HCV was needed.

In this resubmission, the applicant has submitted clinical trial AI444218 (ALLY-3) as the primary evidence of efficacy to support the approval of DCV in combination with Sofosbuvir (SOF) for 12 weeks for the treatment of adults with HCV genotype 3. SOF is a NS5B polymerase inhibitor previously approved in combination with other antiviral agents for HCV. The applicant also cites supportive efficacy and safety data from other clinical trials.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of DCV for the indication proposed. For a detailed discussion of NDA 206843, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background/Regulatory

HCV genotype 3 is responsible for approximately 10% of HCV infections in the U.S. Chronic HCV is a serious and life-threatening disease which can lead to cirrhosis, liver failure, and hepatocellular carcinoma. A pegylated interferon (pegIFN) and ribavirin (RBV) regimen for 24 weeks was the standard of care for chronic HCV genotype 3 until 2011. In 2011, SOF in combination with RBV for 24 weeks was approved for chronic HCV genotype 3. A recent revision to U.S. guidelines for treatment-naïve patients with HCV genotype 3 infection recommends the regimen of SOF with pegIFN and RBV for 12 weeks with SOF and RBV for 24 weeks as an alternative regimen.[1] There are limited

[1] American Association for the Study of Liver Diseases, Infectious Diseases Society of America. *HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C*. Available at: http://www hcvguidelines.org/full-report/initial-treatment-hcv-infection. Accessed July 23, 2015.

approved treatment options and no approved or guideline-recommended treatment options available for patients unable to receive RBV.

3. Product Quality

The Product Quality Review was completed by Dr. Chunchun Zhang. He concluded that there was sufficient information to assure the identity, strength, purity, and quality of the drug product. All manufacturing sites were acceptable. The expiration dating period of 30 months when stored at 25 degrees Celsius is supported by adequate data. The Biopharmaceutics Reviewer, Dr. Sandra Suarez Sharp, found the NDA acceptable. No product quality microbiology issues were identified by Dr. Bryan Riley. No product quality-related PMRs or PMCs were recommended.

I concur that there are no product quality issues precluding approval.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Reviewer, Dr. L. Peyton Myers, found that the submitted studies represented a complete nonclinical toxicology package for DCV and found the NDA acceptable. Nonclinical studies were conducted in the mouse, rat, dog, rabbit, and cynomolgus monkey.

The main findings observed with DCV in the nonclinical studies included liver findings (increased weight and enzyme activity) as well as an adrenal effect (hypertrophy and vacuolation). With respect to liver findings, DCV induced minimal and reversible hepatic changes that included slight increases in serum ALT levels and a minimal increase in liver weights without any liver histologic changes in rats dosed for 1 month. No liver effects were notable in the 6 month study in rats. In monkeys dosed 4 months, liver enzymes (AST, ALT) increased with dose with histological correlates. This was discussed with the Pharmacology Toxicology Reviewer and Team Leader who characterized the nonclinical liver findings as similar to those seen during the development of other direct acting antiviral agents approved for the treatment of HCV.

DCV was neither genotoxic nor carcinogenic in nonclinical studies. Female fertility patterns were not affected with exposure margins at the recommended daily human exposure of 24 fold. All reproductive toxicology findings were assessed by the Reviewer as secondary to maternal toxicity. DCV was excreted in milk at approximately twice the concentration of maternal plasma. These findings are described in labeling.

I concur that there are no non-clinical pharmacology and toxicology issues precluding approval.

5. Clinical Pharmacology

Drs. Stanley Au and Fang Li provided Clinical Pharmacology reviews and found the NDA acceptable. DCV is mainly metabolized by CYP3A and is a P-gp substrate. There

are potential drug interactions which are addressed in labeling. Reduced dosage of 30 mg once daily is recommended with concomitant administration of strong CYP3A inhibitors. Increased dosage of 90 mg once daily is recommended with concomitant administration of moderate CYP3A inducers. Strong inhibitors of CYP3A including phenytoin, carbamazepine, rifampin, and St. John's wort are contraindicated. The risks of adverse reactions or loss of virologic response due to drug interactions is included in labeling in WARNINGS AND PRECAUTIONS. The Reviewers recommended administration with or without food and no dose adjustment for renal impairment. A thorough QT trial was completed for DCV. There was no association of DCV with QT_c prolongation or clinically meaningful effects on other ECG intervals.

The Office of Clinical Pharmacology found that the information in the NDA supports approval of the application. I concur that there are no clinical pharmacology issues precluding approval.

6. Clinical Virology

Drs. Patrick Harrington, Eric Donaldson, and Lalji Mishra provided Clinical Virology reviews.

Based on non-clinical data, DCV has a low resistance barrier in HCV GT3 and activity can be substantially reduced by the presence of 1 or more resistance-associated substitutions in NS5A. The key resistance-associated polymorphism /substitution Y93H alone confers a >3,000-fold reduction in DCV anti-HCV activity in the HCV GT3a replicon system.

The ALLY-3 clinical trial did not allow previous exposure to NS5A inhibitors. Seventeen subjects in the ALLY-3 trial were virologic failures. Of the 17 subjects who experienced virologic failure, 15 (88%) had the Y93H substitution detected at the time of virologic failure. The Y93H substitution was detected as a natural baseline polymorphism in 13/148 (9%) subjects with available data and was associated with reduced efficacy of DCV/SOF in both non-cirrhotic and cirrhotic subjects. Overall, 7/13 (54%) subjects with the Y93H baseline polymorphism achieved SVR12 compared to 124/135 (92%) subjects without the Y93H baseline polymorphism. One subject had the S282T SOF resistance-associated substitution detected at the time of failure. Accumulation of additional NS5A substitutions after virologic failure was minimal in subjects with the Y93H baseline polymorphism, indicating that Y93H polymorphism alone (which causes a > 3,000-fold increase in DCV EC_{50} value) is likely sufficient to confer clinically relevant resistance to DCV in HCV genotype 3 infection. These data are included in labeling.

At this time, a test to screen patients at baseline for the Y93H substitution is not commercially available. As the Y93H polymorphism was observed at baseline in 9% of ALLY-3 participants with available data and participants with the Y93H polymorphism at baseline who failed generally did not accumulate other NS5A substitutions, the review team did not recommend screening as a Limitation of Use in labeling. I agree with this

decision, but note that this may be reconsidered in the future should a test become available.

The Reviewers concluded that the NDA was approvable from a Clinical Virology perspective. They recommended a post-marketing trial in subjects with cirrhosis (see Clinical/Statistical Efficacy below) and a post-marketing study to characterize the long-term persistence of treatment-emergent DCV resistance associated substitutions in HCV genotype 3 infected subjects.

I concur that there are no outstanding Clinical Virology issues that preclude approval and agree with the recommendations above regarding post-marketing studies.

7. Clinical/Statistical Efficacy

Dr. Wen Zang provided the Statistical Review and Dr. Wendy Carter provided the Clinical Review. These Reviewers as well as the CDTL and Division Director concluded that the ALLY-3 trial demonstrated the efficacy of DCV with SOF for the indication proposed. I concur and conclude that the results of the ALLY-3 trial in patients with genotype 3 with supportive evidence of efficacy from clinical trials of DCV in patients with other genotypes provide substantial evidence of efficacy for the indication proposed.

ALLY-3 Trial

The ALLY-3 trial enrolled 152 subjects. Ninety-six percent (146/152) of subjects were from the mainland U.S. and 4% from Puerto Rico. Subjects with compensated cirrhosis were permitted in the trial. Subjects were to receive 12 weeks of DCV 60 mg once daily in combination with SOF 400mg once daily for 12 weeks and were then followed for 24 weeks after treatment. Trial medication was taken with or without a meal. The proposed commercial formulation of DCV and the U.S. commercially available formulation of SOF were used in the trial. The primary efficacy endpoint is sustained virologic response (SVR), defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after discontinuation of treatment (SVR12).

Overall, SVR12 was achieved in 135/152 (89% with 95% confidence interval (CI) of (83%, 93%)) of treated subjects. Of the 17 subjects not achieving SVR12, 1 subject was an on-treatment failure and 16 were relapsers.

Based on non-overlapping confidence intervals, the DCV/SOF 12 week regimen in ALLY-3 was superior to:
SOF/RBV for 12 weeks for genotype 3 subjects in the FISSION study,
PegINF/RBV for 24 weeks for genotype 3 subjects in the FISSION study,
SOF/RBV for 12 weeks for genotype 3 subjects in the FUSION study, and
SOF/RBV for 16 weeks for genotype 3 subjects in the FUSION study.

The Statistical Reviewer Dr. Zeng justified a non-inferiority (NI) margin for the RBV component of the approved regimen of SOF/RBV for 24 weeks. The SVR12 rate for the SOF/RBV 24 week regimen ranges from 60% to 92% depending on treatment experience and cirrhosis status. As SOF monotherapy data is limited by small sample sizes, Dr. Zeng compared the SOF/RBV 24 week regimen with a number of putative placebo regimens with higher SVR12 rates than SOF monotherapy. He concluded that a conservative estimate of the treatment effect (M1) for the RBV component is - 17%. As there is clinical benefit for the DCV/SOF regimen (shorter treatment duration and RBV-free), the CDTL concluded that it would be clinically justified to accept a NI margin of -5% to -10%, and I agree with this conclusion.

Dr. Zeng compared the SVR12 rate for the DCV/SOF regimen in the ALLY-3 trial with the SOF/RBV 24 week regimen. Using a stratum-adjusted Mantel-Haenszel approach to adjust the strata effect of treatment experience and cirrhosis status at baseline, the result is the following:

DCV/SOF - SOF/RBV = 2% with 95% CI of (-4%, 9%)

The lower bound of the 95% CI (-4%) is greater than the -5% to -10% NI margin. Thus, the DCV/SOF 12 week regimen is non-inferior to the SOF/RBV 24 week regimen.

The SVR12 rate was 63% (20/32) with 95% CI of (44%, 79%) for subjects with cirrhosis at baseline, and 96% (115/120) with 95% CI of (91%, 99%) for subjects without cirrhosis at baseline. Given the small sample sizes, the Statistical Reviewer noted that point estimates may be unstable. However, the Statistical Reviewer also noted that confidence intervals for cirrhotics and non-cirrhotics did not overlap.

On April 30, 2015, the applicant submitted two datasets which contained 44 HCV genotype 3 infected subjects with cirrhosis at baseline from the Early Access Program. These data were assessed by the Clinical and Statistical Reviewers as limited and not conclusive.

Reviewers concluded that the data suggests that the DCV/SOF 12 week regimen may not be the optimal regimen for subjects with baseline cirrhosis. A post-marketing requirement will be issued to conduct a trial to determine if a longer duration of treatment or addition of RBV improves the efficacy (i.e., sustained virologic response rate) of DCV with SOF for HCV genotype 3 infected subjects with cirrhosis. In addition, a Limitations of Use statement has been included in labeling that SVR rates are reduced in patients with cirrhosis.

As noted by the Clinical Virology Reviewers, the presence of the Y93H polymorphism at baseline was associated with decreased efficacy. SVR12 rates were comparable for the treatment naïve subgroup compared with the pegIFN/RBV treatment-experienced subgroup. Trends for gender, race, age, and geographic region subgroups were similar to the overall population for SVR12.

Supportive Efficacy Data

The applicant conducted Phase 2 trials which provided dose finding information for DCV, but were also supportive of the efficacy of DCV and provided data regarding the contribution of DCV in a combination regimen. In trial AI444014, 60 treatment naïve genotype 1 subjects received DCV 3 mg, 10 mg or 60 mg once daily in combination with pegIFN/ RBV or placebo + pegIFN/RBV for 48 weeks. SVR12 rates were 42% for the 3 mg group, 92% for the 10 mg group, 83% for the 60 mg group and 25% for placebo + pegIFN/RBV group. In trial AI444010, 395 treatment naïve genotype 1 or 4 subjects received DCV 20 mg or 60 mg once daily in combination with pegIFN/RBV compared to placebo + pegIFN/RBV. The SVR24 rates were 59% and 60% for the DCV 20 and 60 mg groups compared to 38% for the placebo + pegIFN/RBV group.

The original NDA submission provided data from phase 3 pivotal trials: AI447026, AI447028 and AI447029. These trials evaluated the combination of DCV and ASV with and without pegIFN/RBV (DUAL and QUAD regimens) in genotype 1a, 1b, and 4 subjects, and provided supportive evidence of the efficacy of DCV as part of a combination regimen. The overall SVR12 results from the DUAL trials (AI447026 enrolling 222 subjects and AI447028 enrolling 440 patients) was 85% with a range of 80-90%, depending on prior-treatment status of the population. The overall SVR12 rate for the QUAD regimen (trial AI447029) was 94% (372/398) with 95% CI (91%, 96%).

8. Safety

The Clinical Reviewer concluded that the observed safety profile of DCV/SOF is favorable. I concur that there are no safety issues precluding approval. A REMS is not recommended.

The safety database for this NDA resubmission was 1,889 subjects who were treated with the recommended dose of DCV in combination with other anti-HCV drugs in clinical trials. An additional 211 subjects received a DCV/SOF-based regimen in trial AI444040 that evaluated DCV/SOF with or without RBV in HCV GT1, 2, and 3 patients for 12 or 24 weeks. Trial AI444040 was submitted in support of DCV safety and efficacy by the applicant; however, the applicant did not have a right of reference to link the phase 2 formulation of SOF used in this trial to the approved SOF formulation. The AI444040 trial data were reviewed for major safety issues.

In ALLY-3, there were no deaths, no discontinuations due to AEs and only one unrelated on-treatment SAE of GI hemorrhage (due to varices) was reported. The most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. There were no clinically significant trends for laboratory abnormalities. There were no safety findings observed that were associated with race, age, or geographic region.

The WARNINGS AND PRECAUTIONS section of the Prescribing Information will describe a recently identified drug-drug interaction describing the risk of severe, life-

threatening bradycardia associated with use of amiodarone co-administered with SOF in combination with other HCV direct acting antivirals, including DCV. This drug-drug interaction was not identified in the DCV clinical trials (where amiodarone use was prohibited) but was observed in the large expanded access program where DCV was used in combination with SOF with and without RBV and use of amiodarone was allowed. This interaction is discussed in further detail in the Clinical, CDTL, and Division Director reviews. Labeling states that coadministration of amiodarone with DCV in combination with SOF is not recommended; in patients with no alternative treatment options, cardiac monitoring is recommended.

There was a hepatic safety signal identified during the initial review of the NDAs for the combination of DCV and ASV. Based on Phase 2 trials of ASV in combination with pegIFN/RBV, there was a dose-related risk of liver toxicity associated with use of ASV, both in severity and frequency of liver biochemistry abnormalities and adverse events. This was not observed in the DCV Phase 2 trials. Across the Phase 3 trials with the combination of ASV and DCV, drug associated increases in ALT and AST were also observed, most frequently without elevations of bilirubin. However, cases were reported that did have increases in bilirubin and met protocol defined criteria for potential drug-induced liver injury. There was a particularly concerning case of pyrexia, peripheral eosinophilia and significant biopsy proven liver toxicity with eosinophils in trial AI447026 which treated subjects with the DUAL regimen of DCV/ASV and was conducted in Japan. Further assessment found a particular pattern of pyrexia and transient elevation of eosinophils in some Japanese subjects within the first month of exposure to the DUAL regimen which was generally not identified in non-Japanese subjects. Predominately, subjects with pyrexia and transient eosinophilia were not symptomatic and did not have associated liver abnormalities; however, five subjects were identified from trial AI447026 who also had grade 2 or higher increases in ALT.

Overall evaluation of hepatic events for DCV/SOF from ALLY-3 did not reveal any safety signals for liver toxicity. There were no hepatic SAEs, no discontinuations due to serious or nonserious hepatic AEs, no grade 3 or 4 hepatic events, and no subjects met Hy's Law laboratory or clinical criteria. No subjects in ALLY-3 reported hepatic AEs and analysis of liver biochemistry results from subjects in ALLY-3 showed that overwhelmingly, subjects treated with DCV/SOF rapidly normalized their liver biochemistries while on-therapy. There were similar findings in trial AI444040 with no hepatic SAEs, no discontinuations due to hepatic AEs, no grade 3 or 4 hepatic events, and no subjects meeting Hy's Law criteria. Three subjects from trial AI444040 were reported with nonserious hepatic AEs of liver palpable subcostal, hepatic pain, and hepatomegaly.

As the hepatotoxicity signal was seen in the Phase 2 ASV trials but not the Phase 2 DCV trials and was not seen in trials of DCV with other direct acting antivirals except those with ASV, the review team concluded that the hepatotoxicity observed with DCV/ASV based regimens appears related to ASV and not DCV. However, any hepatic concentrated drug may have the potential to cause liver abnormalities in a broad population, particularly one with underlying co-morbidities such as chronic HCV. Post-marketing surveillance will be important. I agree with these conclusions. U.S. Guidelines

for Testing, Managing, and Treating Hepatitis C recommend a hepatic function panel prior to initiating therapy and after 4 weeks of treatment.[2] This standard of care monitoring should be adequate to detect a hepatic safety risk post-marketing.

9. Advisory Committee Meeting

As there were no safety or efficacy issues identified that would likely benefit from Advisory Committee discussion, an Advisory Committee meeting was not held for this resubmission. During the first cycle review of the DCV and ASV NDAs, an Advisory Committee was planned to discuss benefit risk and the hepatic safety concerns. This was cancelled when the ASV NDA was withdrawn.

10. Pediatrics

The applicant has agreed to conduct a study in children ages 3 through less than18 years post-marketing. A waiver will be granted from birth to less than 3 years of age. A PeRC meeting was held on June 3, 2015 and the committee concurred with the deferral and pediatric development plan.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

Noteable labeling issues are discussed above in relevant sections of this memo.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: Approval

Benefit-Risk Assessment:

I conclude that the overall benefit-risk for DCV for use with SOF for the treatment of chronic HCV genotype 3 infection is favorable.

The substantial evidence of efficacy of the 12 week DCV/SOF regimen for the treatment of patients with chronic HCV genotype 3 was established based upon a single adequate and well-controlled trial in genotype 3 patients (ALLY-3) supported by other clinical trials that demonstrated the efficacy of DCV in the treatment of patients with chronic HCV caused by other genotypes as well as the contribution of DCV in a combination regimen. The 12 week DCV/SOF regimen will offer an important treatment option for

[2] American Association for the Study of Liver Diseases, Infectious Diseases Society of America. *HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C*. Available at: http://www hcvguidelines.org/full-report/monitoring-patients-who-are-starting-hepatitis-c-treatment-are-treatment-or-have. Accessed July 23, 2015.

patients. Compared with the regimen of SOF with pegINF and RBV for 12 weeks which is now recommended in Guidelines, this regimen does not require the co-administration of pegINF and RBV, both of which have less favorable adverse event profiles and may not be tolerated by some patients. Compared with the approved SOF and RBV for 24 weeks, this regimen is shorter and does not require the co-administration of RBV.

As DCV is mainly metabolized by CYP3A, there are potential drug interactions leading to contraindications for strong inducers of CYP3A and recommended dose adjustments for a number of co-administered medications. These recommendations are detailed in labeling. Drug interactions are common with direct acting antivirals, and physicians treating patients with HCV commonly refer to labeling for recommendations regarding co-administered medications.

This DCV/SOF 12 week regimen may not be the optimal regimen for subjects with baseline cirrhosis. A Limitations of Use statement is included in labeling to inform physicians that SVR rates are reduced in patients with cirrhosis. The applicant will conduct a trial post-marketing to determine if a longer duration of treatment or addition of RBV improves the efficacy of DCV with SOF for HCV genotype 3 infected subjects with cirrhosis.

The presence of the Y93H polymorphism at baseline is associated with decreased efficacy. This polymorphism is observed at baseline in <10% of genotype 3 patients and ALLY-3 subjects with the Y93H polymorphism at baseline who failed generally did not accumulate other NS5A substitutions. There is no commercially available screening test for this polymorphism at this time. Labeling to mitigate this risk will need to be considered in the future should a test become available. The applicant has agreed to conduct a post-marketing study to characterize the long-term persistence of treatment-emergent DCV resistance associated substitutions in HCV genotype 3 infected subjects.

There is a risk of a drug-drug interaction causing severe, life-threatening bradycardia with coadministration of amiodarone with DCV/SOF. Labeling recommends against co-administration. This risk has been previously reported with SOF, and physicians treating patients with hepatitis C would be expected to be aware of this risk. The applicant has agreed to conduct post-marketing studies that may provide information regarding mechanism.

While there was a hepatic safety signal identified during the initial review of the DCV NDA with the ASV NDA, I agree with the conclusions of the review team that the hepatotoxicity observed with DCV/ASV based regimens appears related to ASV and not DCV. Regardless, any hepatic concentrated drug may have the potential to cause liver abnormalities in a broad population, particularly one with underlying co-morbidities such as chronic HCV. Patients initiating therapy with DCV will have hepatic function testing one month after initiating therapy per standard of care Guidelines. Post-marketing surveillance will be important.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
07/24/2015