CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	May 28, 2015
From	Jeffrey Murray
Subject	Division Director Summary Review
NDA# **Supplement#**	208261 Original
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	May 28, 2015
PDUFA Goal Date	Jan. 28, 2016
Proprietary Name / **Non-Proprietary Name**	Zepatier™ Elbasvir (EBR) and grazoprevir (GZR)
Dosage Form(s) / Strength(s)	Tablet, fixed dose combination of EBR 50mg and GZR 100mg
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic hepatitis C (CHC) genotypes (GTs) 1, 4, or 6 infection in adults
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s)	Treatment of chronic hepatitis GTs 1 or 4 infection in adults

Material Reviewed/Consulted **OND Action Package, including:**	**Names of discipline reviewers**
Medical Officer Review	Sarita Boyd Pharm.D. Prabha Viswanathan M.D.
Statistical Review	Laree Tracy, Ph.D.
Pharmacology Toxicology Review	Chris Ellis Ph.D.
OPQ Review	George Lunn, Ph.D, and team led by Stephen Miller, Ph.D.
Microbiology Review	Takashi Komatsu Ph.D.

	Patrick Harrington Ph.D.
Clinical Pharmacology Review	Su-Young Choi, Pharm,D., Ph.D Luning (Ada) Zhuang, Ph.D Stanley Au, Pharm.D., BCPS
OSI	Antoine El-Hage, Ph.D.
CDTL Review	Adam Sherwat M.D.

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Zepatier (EBR/GZR) is a fixed dose combination (FDC) of 50 mg of elbasvir (EBR) and 100 mg grazoprevir (GZR), two direct-acting antiviral (DAA) drugs with distinct mechanisms of action against hepatitis C virus (HCV). EBR is an NS5A inhibitor and GZR is an NS3/NS4A protease inhibitor. In this NDA, Merck has shown that EBR/GZR (co-administered with ribavirin for some subgroups) is effective for the treatment of chronic hepatitis C (CHC) in patients infected with Genotypes (GT) 1 and 4. The evidence for effectiveness of EBR/GZR as a 12-week regimen was robust with SVR12 (sustained virologic response 12 weeks after cessation of treatment) rates of approximately 95% across multiple patient subgroups including: those with and without cirrhosis, HIV co-infection, chronic kidney disease (CKD) and various levels of prior treatment experience (TE). SVR12 represents a virologic cure and FDA views SVR12 as a validated surrogate endpoint that is associated with a substantial reduction in liver- related morbidity and mortality and all-cause mortality. Therefore the vast majority of patients receiving an EBR/GZR regimen can be expected to have a treatment response that is predictive of a substantial reduction in the risk of liver morbidity and mortality. This treatment benefit greatly outweighs identified risks. Although Merck also proposed an indication for the treatment of CHC with GT6 infection, (b) (4)

The only noteworthy EBR/GZR-related adverse reaction of clinical importance was increased transaminase elevations occurring at or after 8 weeks of treatment initiation in less than 1% of patients receiving the 100 mg dose of GZR (the dose included in the FDC). Elevated transaminases are exposure related and occurred at higher rates and greater degrees of severity in patients receiving higher doses (200 mg to 800 mg) of GZR in Phase 2 development. No patient without cirrhosis or with compensated cirrhosis who received GZR at a dose of 100 mg

developed clinically significant liver toxicity, including those with transaminase elevations. GZR exposures are substantially elevated in decompensated cirrhosis and EBR/GZR will be contraindicated in Child-Pugh B and C cirrhosis due to an increased risk of transaminase elevations and the potential for clinically significant liver toxicity.

Another risk associated with EBR/GZR treatment is the emergence of resistance in patients who relapse after treatment. In clinical trials, HCV with amino acid substitutions conferring resistance to EBR, GZR or both drugs emerged in a majority of patients who experienced virologic relapse. Patients who relapse can develop cross-resistance to other drugs of the same class, jeopardizing future interferon-free treatment options. Analyses of pooled clinical trial data showed that many of the patients who relapsed had certain baseline NS5A polymorphisms (described in this summary review). Patients without baseline NS5A polymorphisms had lower relapse rates and a higher overall SVR12 rate. A longer (16 week) treatment duration and the addition of ribavirin (RBV) in a trial in TE patients, including patients with baseline NS5A polymorphisms, showed a lower relapse rate (0%) compared to relapse rates for 12-week EBR/GZR regimens with or without ribavirin in the same trial and compared to relapse rates of 12 week regimens in other trials. Therefore, it appears that 16 weeks of EBR/GZR plus RBV may be able to overcome the presence of baseline NS5A polymorphisms and resistance emergence may be reduced by screening for NS5A polymorphisms to guide treatment regimen/duration. Two commercial tests for screening NS5A polymorphisms in GT1 patients are presently available.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CHC is a serious and life-threatening disease that can progress to cirrhosis, end-stage liver disease and/or hepatocellular carcinoma and is the most common reason for liver transplantation in the United States • Patients who achieve SVR, a virologic cure, have a marked reduction in the risk of development of complications of end-stage liver disease including need for transplantation.	Treatment of CHC to achieve SVR, virologic cure, should result in a marked reduction in complications of end-stage liver disease in HCV infected individuals. It is expected that treatment of CHC will substantially reduce the need for liver transplantation. In addition, widespread treatment may help to reduce the incidence of new hepatitis C infections if a large proportion of patients are tested and treated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are multiple approved treatments for CHC. Standard of care treatments include DAA regimens (with the addition of ribavirin recommended for some regimens and subpopulations) and expected SVR rates are generally above 90% depending on GT. Regimens range from 12-24 weeks in duration and include several DAA classes. Approved regimens for specific GTs include: Sofosbuvir/ledipasvir (GT 1,4,5,6) Sofosbuvir/daclatasvir (GT 3) Sofosbuvir/simeprevir (GT 1) Sofosbuvir/ribavirin (GT 2,3) Dasabuvir, ombitasvir, paritaprevir/ritonavir (GT1) Ombitasvir, paritaprevir/ritonavir (GT4) • In addition to IFN-free regimens, IFN-based regimens are also available. • There are no approved DAA-based regimens with definitive dosing recommendations for CHC in ESRD patients on hemodialysis	Because multiple treatment options are approved with high SVR rates and acceptable safety profiles, DAVP expects new products will have similarly high levels of efficacy and tolerability. For many GTs the point estimate for SVR12 should approximate 95% or greater. Rates for GT3 and some subpopulations (TE cirrhotics) may be lower, but incremental improvement for future regimens in development is the goal. In addition, tolerability should be such that minimal percentages (< 1-2%) of patients discontinue for toxicity. Risk of liver toxicity is an important concern given underlying liver disease and the difficulty in discerning drug toxicity from underlying disease. Products with low risk of liver toxicity and low risk of drug-drug interactions will have a clinical niche.
Benefit	• Approximately 95% of patients receiving EBR/GZR (with RBV for some subpopulations) in phase 3 trials for GT1 and 4 infections achieved a virologic cure. Results were robust and consistent across many subgroups for GT1. Screening for baseline NS5A polymorphisms and only treating patients without polymorphisms with a 12 week regimen of EBR/GZR may further improve SVR rate to approximately 98% • Limited data suggest the addition of RBV and extending EBR/GZR treatment 4 weeks longer (total, 16 weeks) may be able to overcome the effect of baseline NS5A polymorphisms on virologic relapse	The vast majority of patients who receive EBR/GZR are expected to benefit in terms of achieving a virologic cure. Virologic cure is estimated to provide a 50% or greater reduction in risk of progression to end stage liver disease and liver related mortality[1]. The long term benefits, especially with respect to liver mortality, are substantial, especially considering the short duration of treatment (12-16 weeks).

[1] Hepatology Aug 2015; Hamish A. Innes, Scott A. McDonald

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Data were limited for GT4 patients who were TE with PR but data from GT1 TE patients help to support a dosage regimen recommendations.	
Risk	• The only important adverse reaction identified was liver toxicity manifested by transaminase elevations occurring in approximately 1% (12/1558) of patients overall. Most resolved either on or off treatment. Only one of the twelve patients had clinical symptoms and no patient receiving the 100 mg dose of GZR included in the FDC had clinically serious liver toxicity. One patient with Child-Pugh B cirrhosis (decompensated cirrhosis), for which EBR/GZR is contraindicated, had further liver decompensation resulting in death, although it was attributed to the patient's underlying disease and not attributed to drug. This patient did not have characteristic transaminase elevations associated with GZR. • It is unknown whether a subset of individuals with transaminase elevation could progress to more clinically significant liver toxicity but, based on the clinical trial data, it is likely that this would occur in less than 10% of patients experiencing transaminase elevations or less than 0.1% overall. • A small percentage of patients will not achieve SVR12 due to relapse and will have a high probability of developing additional resistance to NS5A inhibitors and resistance protease inhibitors or both classes, potentially jeopardizing the ability to have future successful treatment responses with an interferon-free regimen. Patients at greatest risk of relapse and drug resistance are those with baseline NS5A polymorphisms.	Although not identified in clinical trials, there is a potential risk for clinically serious liver toxicity stemming from transaminase elevations. Based on the safety database one would not expect this adverse reaction to occur at a rate of more than 1/1000 patients at the 100 mg dose of GZR. Increased GZR exposures secondary to hepatic impairment or drug-drug interactions could increase this risk. The expected benefit in virologic cure and resulting reduction in liver mortality is expected to outweigh substantially the potential risk of clinical relevant liver toxicity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The risk of transaminase elevations and potential liver toxicity is discussed in the Warnings section of the label. Physicians are instructed to obtain laboratory evaluations at week 8 of treatment and at week 12 of treatment for patients treated with a 16-week regimen. • Contraindications and drug-drug interaction data in the label inform physicians on how to avoid situations in which increased GZR exposures could lead to an increased risk of liver toxicity. • Screening for baseline NS5A polymorphisms and using a regimen of EBR/GZR plus RBV for 16 weeks may overcome reduced susceptibility and reduce the risk of relapse and further emergence of resistance.	A formal risk evaluation and mitigation strategy (REMS) for this application will not be required. Labeling information and instructions in the prescribing information should help to optimize virologic response rates (SVR), reduce the rate of emergence of resistance and mitigate the risks of liver toxicity and increased GZR exposures resulting from drug-drug interactions.

2. Background

Merck submitted this NDA for a FDC tablet (trade name Zepatier) containing two direct-acting antivirals (DAAs), EBR and GZR, for the treatment of CHC for HCV GTs 1, 4 and 6. Merck proposes that one tablet of EBR/GZR, 50mg/100 mg, be administered once daily with the addition of RBV for certain subpopulations. EBR is an NS5A inhibitor[2] and GZR is an NS3/4A protease inhibitor, two DAAs with distinct mechanisms of action. FDA has approved two other NS5A inhibitors and four other NS3 protease inhibitors for use with other antiviral agents for the treatment of CHC. EBR/GZR as an FDC or as single approved products is not yet approved in any country.

There are six[3] HCV GTs worldwide but the vast majority (>90%) of patients in the U.S. are infected with GT1, 2 or 3, with GT1 being the most common. GTs are further subdivided into subtypes, such as GT1a and GT1b. Optimal treatment regimens and durations for previously approved DAAs vary according to GT, GT subtype, and baseline host characteristics such as, presence or absence of cirrhosis and previous treatment experience. Drug development of EBR/GZR focused primarily on GT1 infection (the most common GT in the U.S.), with much fewer GT4- and GT6-infected patients participating in clinical trials.

Recommended regimens for CHC treatment for all GTs no longer require the use of interferon (IFN); however, ribavirin (RBV) is still recommended for certain GTs or host subpopulations. The clinical expectation is that DAA-based hepatitis C regimens will yield virologic cure rates, or SVR12, exceeding 90% for most GTs and exceeding 95% for certain populations and GTs.

Approved interferon-free regimens for specific GTs include:

- Sofosbuvir/ledipasvir (GT 1,4,5,6)
- Sofosbuvir/daclatasvir (GT 3)
- Sofosbuvir/simeprevir (GT 1)
- Sofosbuvir/ribavirin (GT 2,3)
- Dasabuvir, ombitasvir, paritaprevir/ritonavir (GT1)
- Ombitasvir, paritaprevir/ritonavir (GT4)

Some patients harbor HCV with one or more genetic polymorphisms (amino acid substitutions or variants) that could affect drug susceptibility to one or more drugs of a class even without prior exposure to DAAs. Polymorphisms are often the predominant circulating virus at baseline unlike resistance substitutions which exist as a minority species until selected to circulate as the predominant virus in the setting of drug pressure and incomplete viral suppression. Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. Polymorphisms in the NS5A protein occur in a minority of patients, typically 5-15%, but may substantially impact virologic response and/or choice of some drug regimens. In this NDA the effect of baseline NS5A

[2] The NS5A encoded gene product is a non-enzymatic protein, which is essential for viral genome replication and virus assembly.
[3] a seventh genotype has been identified but is considered rare.

polymorphisms on SVR12 was analyzed and certain NS5A polymorphisms were identified that had a substantial effect on SVR12.

Earlier in development of EBR and GZR, the IND for GZR was placed on partial clinical hold because of dose-related GZR liver toxicity. Trial participants receiving daily GZR doses of 200-800 mg, in combination with PR, experienced transaminase elevations after approximately 8 weeks of treatment. Merck determined that 100 mg of GZR would be a reasonably safe dose, with a lower risk for transaminase elevations, to study in phase 3 trials and the partial hold was lifted.

At the time of NDA submission, EBR/GZR had breakthrough therapy (BT) designations for the treatment of patients with concomitant CHC and end stage renal disease (ESRD) on hemodialysis (HD) and for CHC with GT4 infection. FDA granted BT designation for these patient groups in April 2015.

3. Product Quality

NDA 208261 was recommended for approval from the Product Quality perspective by the review team headed by Dr. Stephen Miller. There are no unresolved product quality issues precluding approval. All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance have determined these facilities to be acceptable.

4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology/Toxicology review prepared by Chris Ellis, Ph.D. who concurs with approval of EBR/GZR for the treatment of CHC as recommended in the prescribing information.

In brief, Merck conducted a complete pharmacology toxicology program including repeat-dose toxicology studies for EBR and GZR in mice, rats and dogs.

For EBR, no target organs of toxicity were identified following oral administration in mice, rats and dogs in studies of 1, 6 and 9 months, respectively, at the following exposure (AUC) multiples exceeding predicted human exposures of EBR/GZR 50mg/100mg: 55 (in mice), 9 (in rats) and 8 (in dogs).

For GZR, the main target organs of toxicity were liver and gallbladder (mice and dogs). Hepatobiliary findings included increased total (direct) bilirubin, ALT, AST, ALP (dogs) and increased hepatocellular size and liver weights. In mice, ALT, AST and bilirubin elevations occurred after approximately 2 weeks of GZR administration and resolved 8 weeks into the treatment-free "recovery" period with no histopathological effects noted following the recovery period. In dogs, microlithiasis in the gallbladder lumen, enlarged liver bile ducts, distended gallbladders, and thickening of the gallbladder wall were also observed. Other target organs of toxicity were of questionable clinical relevance because of the high human exposure (AUC) multiples for which toxicity in animals was observed: 163 for testes, 282 for gut and 747 for renal and hematologic.

As stated in the prescribing information, "No effects on mating, female or male fertility, or early embryonic development were observed in rats up to the highest dose tested."

EBR and GZR were not mutagenic or clastogenic as tested in the Ames assay, the in vitro chromosomal aberration assay in CHO cells and an in vivo rat micronucleus assay. Dr. Ellis states, "Mouse and rat carcinogenicity studies with EBR and GZR are not being conducted, given the intended treatment duration (<6 months) and lack of a specific cause for concern."

5. Clinical Pharmacology

The clinical pharmacology review team for this NDA was: Su-Young Choi, Pharm,D., Ph.D; Luning (Ada) Zhuang, Ph.D; Stanley Au, Pharm.D., BCPS. The team concurs with approval of EBR/GZR for the treatment of CHC as recommended in product labeling.

This memo will only focus on key issues of the clinical pharmacology review as pertains to important approval and labeling issues. In brief, both GZR and EBR are substrates of P-gp and are metabolized by CYP3A4. GZR is a substrate of hepatic uptake transporters, OATP1B1/3. The primary route of excretion of both drugs is feces and less than 1% of the administered dose is excreted in urine. The mean elimination half-lives of GZR and EBR are approximately 31 hours and 24 hours respectively and allow for once daily dosing. Food does not substantially affect exposures of either drug, such that EBR/GZR can be taken without regard to meals. In thorough QT studies, neither drug prolonged the QTc interval.

Exposure-response and exposure-safety relationships helped to define exposure thresholds/boundaries for safety and efficacy when considering intrinsic factors (such as hepatic impairment, gender, and race) and extrinsic factors (such as drug-drug interactions) that affect exposures (AUC) of EBR and GZR. Therefore, choice of doses and PK/PD relationships are discussed first in this memo, followed by considerations for intrinsic and extrinsic factors.

Choice of Doses: Exposure-Efficacy and Exposure Safety Analyses

GZR

A Phase 2 GZR dose-ranging trial showed no differences in efficacy for GT1 across GZR doses ranging from 100 to 800 mg when administered with Peg-IFN and RBV (PR). However, transaminase elevations occurred at higher rates with doses of 200 mg or greater compared to the 100 mg dose. Due to exposure-related transaminase elevations, GZR dosing was capped at 100mg QD in Phase 3 trials. A small trial of 25, 50 and 100 mg QD GZR in combination with PR demonstrated similar SVR12 rates at 50 mg (21/25, 84%) and 100 mg (23/26, 89%), but a lower response for 25 mg (13/24, 54%). Therefore 100 mg QD of GZR was selected for study in Phase 3 as a dose with what Merck and DAVP agreed would be an appropriate balance of safety and efficacy.

A Phase 1b EBR monotherapy dose-ranging trial showed that 50 mg EBR had similar antiviral activity as 10mg for GT1 overall, but that 50 mg may have provided more sustained suppression than 10 mg for GT1a patients. In a Phase 2 dose-ranging trial, 50 mg QD of EBR produced efficacy that was similar to 20 mg QD when given with 100 mg QD GZR and RBV

for 12 weeks. In addition, the trial did not identify dose-related toxicities for EBR; therefore, 50 mg of EBR was selected as the dose for Phase 3 to allow a margin for potential decreases in EBR exposure (e.g., from drug-drug interactions) without affecting efficacy.

Merck and the clinical pharmacology reviewers conducted additional exposure-response analyses pooling data from seven Phase 2/3 studies in which GZR and EBR were co-administered with and without RBV in patients infected with HCV GT1, 4, or 6. The analyses showed that GZR exposure was not a significant predictor of SVR12; however, EBR exposure was a significant predictor of SVR12 particularly for patients with baseline NS5A polymorphisms. Other significant predictors of treatment response were treatment duration, baseline HCV RNA levels, and presence of baseline polymorphisms in NS5A. Of these factors, the presence of baseline NS5A polymorphisms was the most important predictor of treatment response and will be discussed more fully under Clinical Efficacy below.

Exposure-safety

The exposure-safety analysis pooled data from thirteen Phase 2/3 studies and included GZR doses from 25 to 800 mg QD and focused on the occurrence of transaminase elevations (typically occurring after 8 weeks) because this was identified as a dose-related toxicity in the previously mentioned GZR trials. The observed rate of transaminase elevations from patients in a "reference" population, consisting of non-Asian subjects without cirrhosis or severe chronic kidney disease (CKD), administered 100 mg GZR was 0.5% (7/1273). Increases in GZR exposures of 5-fold (GZR 200 mg) and ~13 to 14-fold (GZR 200 to 400 mg) that of the reference population are predicted to result in transaminase elevation event rates of ~2% and ~5%, respectively.

The clinical pharmacology review team conducted an independent assessment of the exposure-response relationships between transaminase elevations and GZR exposure and concluded that a 3-fold upper bound would be an appropriate exposure threshold from a safety perspective. A 3-fold increase in GZR exposure would be expected to result in a median transaminase elevation event rate of 1.2% with an upper bound of 3% (90% CI). With respect to drug-drug interactions, a somewhat conservative threshold was chosen to allow for further exposure increases that could result from other concomitant factors (such as race or gender).

Hepatic Impairment

Establishing the pharmacokinetic (PK) profile in patients with varying degrees of hepatic impairment is critical for CHC treatments, particularly for drugs that are metabolized by the liver. GZR and EBR PK were evaluated in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment (Child-Pugh Classes A, B, and C, respectively). In addition, Merck conducted population PK analyses in patients without cirrhosis and with compensated cirrhosis (Child-Pugh A) in Phase 2 and 3 trials. GZR exposures (AUC24hr) were increased by 1.7-fold, 4.8-fold and 11.7-fold, in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to healthy volunteers. Similarly, population PK analyses showed that GZR AUC was approximately 65% higher in patients with mild hepatic impairment compared to non-cirrhotic patients. As stated in the Clinical Pharmacology review, the magnitude of the increased GZR exposure in patients with mild

hepatic impairment is not considered clinically relevant. However, substantial increases in GZR exposures in subjects with moderate and severe hepatic impairment may increase the risk of transaminase elevations.

EBR AUC values were decreased by 40%, 28%, and 12% in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to matched healthy volunteers. However, there was no significant difference between subjects with mild hepatic impairment vs. those without cirrhosis in population PK analyses.

Renal Impairment

PK in renal impairment is an important issue for this NDA. Although neither GZR nor EBR are significantly excreted via the kidneys, a substantial proportion of patients with end stage renal disease (ESRD) have HCV infection. Also EBR/GZR was granted BT designation for the ability to treat CHC patients with renal impairment, an unmet medical need.

Merck evaluated GZR and EBR PK in non-HCV-infected subjects with severe renal impairment (eGFR < 30 mL/min) and ESRD (subjects on hemodialysis). In addition, Merck conducted population PK in CHC patients with severe renal impairment (n=30) and ESRD (n=92) who enrolled in a Phase 3 trial (C-SURFER), more fully described in the Clinical Efficacy section of this review. GZR and EBR AUCs were 65% and 86% higher in non-HCV-infected subjects with severe renal impairment as compared to matched healthy volunteers. No significant differences in EBR or GZR exposures were observed in non-HCV-infected subjects with ESRD receiving hemodialysis (HD) as compared to matched healthy volunteers. Similar results were observed in population PK analyses and the differences in exposures are not considered clinically relevant. EBR/GZR can be used in patients with severe renal impairment or ESRD receiving HD.

Gender, age, and race

In population PK analyses, GZR AUCs were estimated to be 30% higher in females as compared to males, 50% higher in Asian as compared to White patients, and 45% higher in the elderly (≥ 65 years old) as compared to young (< 65 years old) patients. Of note, the observed event rates of transaminase elevations were higher in Asians, elderly, or female patients as compared to White, young, or male patients, respectively.

In population PK analyses, EBR AUCs were estimated to be 50% higher in females as compared to males, 15% higher in Asians as compared to White, and 16% higher in elderly (≥ 65 years old) as compared to young (< 65 years old) patients.

Drug-Drug Interactions (DDI)

Refer to the label posted with this Summary Review for DDI information and drugs that are not recommended or contraindicated for concomitant use with EBR/GZR. Because both drugs are metabolized via CYP3A4 and GZR is a substrate of OATP1B1/3, multiple significant drug interactions are expected. Thresholds for avoiding concomitant use with other drugs were based on exposure-safety analyses in which greater than 3-fold increases in drug exposures on GZR increased the risk of transaminase elevations. Drugs that were absolutely contraindicated met a GZR exposure-increase threshold of 10-fold and those that were not recommended met a GZR exposure increase threshold of 3-fold. The review team also concluded that the co-

administration of ZEPATIER with OATP1B1/3 inhibitors, strong CYP3A4 inducers, or efavirenz warrant a contraindication.

6. Clinical Virology

Please refer to the joint virology review by Takashi Komatsu Ph.D. and Patrick Harrington Ph.D. for a detailed assessment of the non-clinical and clinical virology data. The Clinical Virology reviewers concur with approval of EBR/GZR for the treatment of CHC as recommended in the prescribing information.

The major Clinical Virology issues are: 1) the development of resistance-associated substitutions in patients who fail to achieve SVR12, primarily due to relapse, and how resistance emergence can affect the response of subsequent regimens for drugs of the same class, and 2) the effect of baseline polymorphisms on SVR12. The latter is discussed further in the Clinical Efficacy section of this review.

Assessments for resistance in cell culture were used to guide clinical virology assessments. NS5A amino acid substitutions selected in HCV GT1a replicon systems under drug pressure with EBR included Q30D/E/H/R, L31M/V and Y93C/H/N which reduced cell culture antiviral activity by 6- to 2,000-fold. In GT1b replicon systems, NS5A substitutions under EBR pressure occurred at L31F and Y93H which reduced cell culture antiviral activity by 17- to 67-fold. In GT4 replicon systems, NS5A substitutions under EBR pressure occurred at L30S, M31V, and Y93H which reduced cell culture antiviral activity by 2- to 23-fold. Selection of HCV genotype 1a replicons with GZR resulted in single NS3 substitutions D168A/E/G/S/V which reduced cell culture antiviral activity by 2- to 81-fold. Selection of HCV genotype 1b replicons resulted in single NS3 substitutions F43S, A156S/T/V, and D168A/G/V which reduced cell culture antiviral activity by 3- to 375-fold. Selection of HCV genotype 4 replicons resulted in single NS3 substitutions D168A/V which reduced cell culture antiviral activity by 110- to 320-fold.

Using data pooled from subjects treated with EBR/GZR with or without RBV in Phase 2 and 3 clinical trials, Merck and FDA reviewers analyzed the emergence of resistance in 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent NS5A substitutions were detected in 30/37 (81%) GT1a-, 7/8 (88%) GT1b-, and 5/5 (100%) GT4-infected patients. The most common treatment-emergent NS5A substitution in GT1a was at position Q30 (n=22). Treatment-emergent NS3 substitutions were detected in 29/37 (78%) GT1a, 2/8 (25%) GT1b, and 2/5 (40%) GT4-infected subjects. The most common treatment-emergent NS3 substitution in GT1a were at position D168 (n=18). Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) GT1a, 1/8 (13%) GT1b, and 2/5 (40%) GT4 infected subjects.

7. Clinical/Statistical-Efficacy

Refer to the reviews provided by the Clinical Reviewers, Sarita Boyd Pharm.D., Prahba Viswanathan M.D.; the Statistical Reviewer, Laree Tracy Ph.D; and the CDTL Adam Sherwat M.D. for additional details on Clinical Efficacy and Safety. The review team concurs with approval of EBR/GZR for the treatment of CHC. Based on their reviews and my assessments, the Applicant has provided substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of EBR/GZR for the treatment of CHC in patients with GT1 and GT4 infection.

The principal trials (Phase 3) that supported efficacy, safety and dosing recommendations are listed in Table 1. The Phase 3 development program evaluated patients who were treatment naïve (TN), treatment experienced (TE), HIV co-infected, and those with CKD. Patients with and without cirrhosis were evaluated in all of the trials listed in Table 1.

Previous treatment experience was limited to pegylated-interferon and ribavirin (PR) in trial C-EDGE TE but included PR plus a protease inhibitor (PI) in C-SALVAGE.

Table 1. Principal Trials Supporting Efficacy and Safety

Trial Name	Population	Trial Arms
C-EDGE TN	GTs 1, 4, 6 TN only	EBR/GZR*: 12 wks (n=316) Placebo: 12 wks (n=105)
C-EDGE TE	GTs 1, 4, 6 TE to PR only HIV co-infected included	EBR/GZR: 12 wks (n=105) EBR/GZR: 16 wks (n=105) EBR/GZR + RBV#: 12 wks (n=104) EBR/GZR + RBV: 16 wks (n=106)
C-EDGE COINFECTION	GTs 1, 4, 6 TN only HIV co-infected only	EBR/GZR: 12 wks (n=218)
C-SURFER	GT1 CKD TN and TE	EBR + GZR:12 wks (n=122) Placebo: 12 wks (n=113)
C-SALVAGE	GT1 TE to PR+PI	EBR + GZR + RBV: 12 wks (n=79)

*EBR/GZR indicates the FDC formulation was used. EBR+GZR indicates that the individual formulations were used.
RBV was dosed according to weight

The rationale for the doses of EBR and GZR chosen for Phase 3 trials and for the FDC tablet was discussed in the Clinical Pharmacology section above. Based on Phase 2 data, 12 weeks of EBR/GZR without RBV appeared to be sufficient for TN patients. Two treatment durations (12 and 16 weeks) and/or the addition of RBV were evaluated in trials that enrolled TE patients.

Factorial designs comparing EBR/GZR to each of the drugs alone were not conducted because it is known from many published investigations that a single drug for the treatment of CHC is not sufficient and could result in drug resistance resulting in class resistance and loss of therapeutic options. Therefore the Fixed Drug Combination rule has been satisfied for this application.

The trial designs in the Phase 3 development program were in alignment with draft guidance[4] and DAVP's recommendations during milestone meetings with Merck. Two of the trials listed above, C-EDGE TN and C-SURFER were placebo controlled (actually delayed treatment because participants randomized to placebo received treatment after the trial blinds were broken). The placebo arms for these trials were included primarily to provide a controlled safety evaluation of the two-drug regimen compared to placebo. Placebo controls also allowed a comparison of efficacy for the regimen as a whole; however, spontaneous clearance of HCV in CHC is rare and no virologic clearance is expected on patients receiving placebo. The other trials were designed to compare SVR12 to historical rates from previously conducted trials of regimens that were considered a standard of care at the time the Merck trials were initiated (refer to the statistical review prepared by Laree Tracy for details). Comparisons to historical rates are considered appropriate for these trials because: 1) SVR12 is a highly objective endpoint, 2) SVR12 rates were expected to exceed 90% and if demonstrated to be above 90% would be considered a clinically useful option for clinicians independent of response rates for other approved options, 3) for populations such as previous PR+PI failures (C-SALVAGE), there is no active control available.

SVR12 was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) 12 weeks after the cessation of treatment.

Although three of the Phase 3 trials included GT1, 4 and 6 patients, the vast majority of trial participants were infected with GT1. DAVP's thinking regarding enrollment of multiple GTs in a single trial has evolved since the last draft guidance was published and since DAVP provided advice to Merck on their Phase 3 trials. While DAVP understands that there are logistical advantages to enrolling multiple GTs in the same trial, we believe it is important to analyze SVR rates for each genotype separately because response rates among GTs vary and sometimes treatment regimens or duration differ. Clinicians are also interested in knowing SVR rates for each GT separately. For these reasons, DAVP asked Merck to display in product labelling SVR rates for each GT separately.

GT1 Efficacy

Table 2 shows SVR12 rates in three trials for GT1 infected patients according to subtype and presence or of absence of cirrhosis.

Table 2. GT1: Treatment Naïve Patients

	C-EDGE TN	C-EDGE COINFECTION	C-SURFER (CKD)
GT1 Overall	95% (273/288)	95% (179/189)	94% (115/122)
GT1a	92% (144/157)	94% (136/144)	97% (61/63)
GT1b	98% (129/131)	96% (43/45)	92% (54/59)
GT1 No Cirrhosis	94% (207/220)	94% (148/158)	95% (109/115)
GT1 Cirrhosis	97% (66/68)	100% (31/31)	86% (6/7)

[4] FDA draft guidance for industry, Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral for Treatment.

In summary for TN patients, SVR12 for GT1 was 95% with slightly higher rates for 1b and slightly lower rates for 1a, which is consistent with other DAAs. Relapse rates for TN GT1 patients were 3% except for the trial in patients with CKD in which the relapse rate was <1%. It is noteworthy and unexpected that SVR12 rates were numerically higher in patients with cirrhosis compared to those without cirrhosis. This may be a chance occurrence, a result of the relatively small sample size of patients with cirrhosis, or possibly related to another factor such as higher GZR exposures in patients with mild hepatic impairment (Child-Pugh A cirrhosis).

For TE GT1 patients who had failed PR regimens, SVR12 rates were similar (93-97%) for the four treatment arms in C-EDGE TE and similar to rates observed in TN patients. Top-line results are summarized in Table 3. The 16-week arm with RBV had the lowest numerical relapse rate; however, similarly low relapse rates were observed in the other three arms among patients without baseline NS5A polymorphisms (data not shown). This suggests that 16 weeks plus RBV is only needed for patients with baseline N5A polymorphisms and not for all TE patients.

Table 3. C-EDGE TE: SVR12 and Virologic Failure Rates in GT1

Treatment Arm	EBR/GZR 12 weeks (n=96)	EBR/GZR+RBV 12 weeks (n=89)	EBR/GZR 16 weeks (n=96)	EBR/GZR+RBV 16 weeks (n=96)
SVR 12	93% (89/96)	94% (84/89)	95% (91/96)	97% (93/96)
Virologic Failure	5% (5/96)	6% (5/89)	4% (4/96)	0

Therefore, EBR/GZR for 12 weeks without RBV will be recommended for PR TE patients without baseline polymorphism and EBR/GZR for 16 weeks with RBV for TE patients with baseline NS5A polymorphisms and EBR/GZR for 12 weeks

For TE patients who failed a PR plus PI regimen, the only regimen studied (12 weeks of EBR/GZR + RBV) in C-SALVAGE yielded an SVR12 of 96% also similar to the rate in TN GT1 patients with EBR/GZR alone.

Efficacy in GT1: Subgroup Analyses

Among the principal efficacy trials, no significant differences in efficacy were noted with respect to the following baseline factors: age, gender, race, geographical region, prior PR treatment history, cirrhosis status, or HIV co-infection. However, one baseline factor that clearly affected response rates for GT1a infected patients was the presence of certain baseline NS5A polymorphisms. In fact, most of the virologic relapses were explained by the presence of one or more of four baseline polymorphisms. DAVP reviewers considered this to be an important review issue and this became one of the primary issues for resolution.

Baseline NSA polymorphisms did not appear to appreciably effect SVR12 for GT1b patients. In genotype 1a-infected subjects, the NS3 Q80K polymorphism did not impact treatment response and polymorphisms at other NS3 resistance-associated positions were uncommon and were not associated with reduced treatment efficacy for GT1a or 1b.

Genotype 1a: SVR by Baseline NS5A Polymorphisms

Table 4 shows SVR12 rates for data pooled from Phase 2 and 3 trials for GT1a-infected subjects according to the presence of one or more NS5A amino acid polymorphisms at positions M28, Q30, L31 or Y93. The prevalence of polymorphisms at any of these positions in GT1a-infected subjects in the U.S was 12% (37/308). Reduced efficacy in patients with these polymorphisms receiving a 12-week regimen of EBR/GZR for 12 weeks was observed regardless of prior treatment history or cirrhosis status. Patients with a polymorphism at M28 had a less pronounced diminution of SVR12 rates than those with the other three polymorphisms. Most patients who relapsed had virus isolates with additional substitutions conferring resistance to NS5A inhibitors, HCV PIs or both classes. Resistance-associated substitutions may be long-lived and may affect response to future treatments.

Table 4: Efficacy of 12 Week Regimens of EBR/GZR in HCV Genotype 1a-Infected Subjects with or without NS5A Resistance-associated Polymorphisms

NS5A Polymorphism*	Prevalence of Polymorphism	SVR12 with Polymorphism	SVR12 without Polymorphism
M28[#]	6% (33/506)	88% (29/33)	95% (451/473)
Q30[†]	2% (11/561)	40% (4/10)	96% (476/496)
L31[‡]	3% (15/561)	38% (5/13)	96% (475/493)
Y93[§]	2% (10/561)	63% (5/8)	95% (475/498)
M28, Q30, L31 or Y93	11% (62/561)	70% (39/56)	98% (441/450)

*Any change from GT1a reference.
[#]SVR12 rates for polymorphisms at M28: M28L (100%; 1/1), M28V (86%, 25/29), M28T (100%; 3/3)
[†]SVR12 rates for polymorphisms at Q30: Q30H (20%; 1/5), Q30L (50%, 1/2), Q30R (67%; 2/3)
[‡]SVR12 rates for polymorphisms at L31: L31M (38%, 5/13)
[§]SVR12 rates for polymorphisms at Y93: Y93C (100%, 3/3), Y93H (33%; 1/3), Y93N (100%, 1/1), Y93S (0%; 0/1)

As discussed above, C-EDGE TE was the only Phase 3 trial that included longer treatment durations (16 weeks) of EBR/GZR with or without RBV. In this trial, no GT1 patient and specifically no GT1a patient experienced virologic relapse including those patients with baseline polymorphisms (Table 5, data pooled from Phase 2 and 3 for 12 week regimens). The number of patients with baseline polymorphisms is limited (n=6); however, the data are promising that this more intensive regimen may be sufficient to overcome reductions in susceptibility conferred by the presence of baseline polymorphisms. More data is needed to confirm these findings; however, it is reasonable to recommend the use of more intensive treatment regimen (4 weeks longer and the addition of ribavirin) for a small subset of patients (~11%) until additional data can be evaluated in the form of a post-marketing requirement (see Post-marketing Section).

Table 5: Efficacy of ZEPATIER for 12 Weeks or ZEPATIER with Ribavirin for 16 Weeks in HCV Genotype 1a-Infected Subjects with or without NS5A Resistance-associated Polymorphisms

	ZEPATIER 12 Weeks (pooled data)		ZEPATIER + RBV 16 Weeks (C-EDGE TE)	
NS5A Polymorphism	SVR12 with Polymorphism % (n/N)	SVR12 without Polymorphism % (n/N)	SVR12 with Polymorphism % (n/N)	SVR12 without Polymorphism % (n/N)
M28*, Q30*, L31* or Y93*	70% (39/56)	98% (441/450)	100% (6/6)	100% (49/49)

*Any change from GT1a reference.

In genotype 1b-infected subjects treated with ZEPATIER for 12 weeks, SVR12 rates (non-virologic failure-censored) were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A polymorphisms at position 28, 30, 31 or 93. In genotype 1b-infected subjects, baseline polymorphisms did not appreciably impact treatment response to warrant screening.

Efficacy in GT4

In a pooled analysis of TN GT4 infected patients receiving 12 weeks of EBR/GZR (no ribavirin) in C-EDGE TN, C-EDGE TE and a phase 2 trial (C-SCAPE), SVR12 was 97% (64/66%), similar to that of GT1.

For TE GT4 patients, there were only limited data (37 patients overall) from the C-EDGE TE trial in which patients were randomized to one of four regimens (12 or 16 weeks of EBR/GZR with and without RBV). In the 4 treatment arms SVR12 rates ranged from 60%-100% with the highest numerical response in patients receiving 16 weeks of EBR/GZR plus RBV (100%, 8/8). Given the small numbers of GT4 TE patients, DAVP leveraged data from GT1 TE patients receiving 16 weeks of EBR/GZR plus RBV in the trial C-EDGE TE which yielded SVR12 rates that were similar to those seen with GT1 TN patients receiving EBR/GZR and appeared to reduce relapse rates even for GT1a infected patients with baseline polymorphisms. It is reasonable to leverage supporting data from GT1 in this situation because GT4 appears to be no more difficult to treat than GT1 across various treatment programs and in some cases has required fewer drugs. Also in Merck's trials, EBR/GZR performed similarly in TN patients with GT1 and GT4 infection. It is important to consider that only a small percentage of U.S. CHC patients are infected with GT4 and that the TE subgroup of GT4 patients is still smaller and shrinking (as patients who failed PR will be successfully retreated with other regimens). DAVP considered that it would not be feasible to further investigate a subgroup that will soon be obsolete (with available retreatments) and instead opted to recommend a conservative regimen (longer duration with RBV) based on limited GT4 TE data and supportive data from GT1 TE patients.

In genotype 4-infected subjects, the SVR12 rate was not reduced for subjects with baseline NS5A polymorphisms (100%, 28/28).

(b) (4)

(b) (4)

8. Safety

The safety database for EBR/GZR was adequate to assess safety for the proposed indications and recommended dosage regimens. The safety database included 1747 subjects who received GZR 100 mg and EBR 50 mg for at least 12 weeks, and 360 subjects who received GZR 100 mg and EBR 50 mg for 16-18 weeks. It should be noted that safety data generated for one GT can be used to support the safety in other GTs.

Fatigue, headache, and nausea were the most common adverse events (AEs) reported across trials of EBR/GZR (without RBV), but these events occurred at similar rates in the placebo arm of C-EDGE TN. One percent (10/954) of subjects in the Phase 3 trials receiving EBR/GZR (with or without RBV) discontinued study drug due to an AE.

With respect to serious AEs (SAEs) and deaths, there were no treatment-emergent deaths that were considered to be likely related to EBR/GZR (refer to Dr. Boyd's review for details). The rate of SAEs across the trials listed in Table 1 (excluding C-SURFER in CKD and C-SALVAGE) was less than 4% and similar to the rate in the placebo group from C-EDGE TN. As expected, the rate of SAEs and deaths was higher in the trial in CKD than in the other Phase 3 trials but occurred at a similar rate in the treatment arm and placebo arms. One notable SAE occurring one week after initiation of EBR/GZR was increasing creatinine levels with a kidney biopsy that showed interstitial nephritis judged as drug-related by the investigator. It is difficult to assess whether this single case of interstitial nephritis without reports of renal toxicity in other patients represents a safety signal for EBR/GZR; however, interstitial nephritis and other types of renal injury will continue to be assessed during post-marketing pharmacovigilance.

With respect to laboratory abnormalities, transaminase elevations was the primary safety signal of interest and are discussed below under hepatotoxicity. In addition creatinine kinase (CK) elevations (all grades) occurred in more subjects treated with EBR/GZR (9%) compared to placebo (6%); the majority of CK elevations in EBR/GZR-treated subjects were grade 1 (6%) or grade 2 (2%).

Hepatotoxicity

Merck identified GZR dose-related transaminase elevations in Phase 2. Transaminase elevations > 2-fold the upper limit of normal (ULN) occurred in 4%, 3%, 21%, and 24% of subjects randomized to 100, 200, 400, and 800 mg daily of GZR, respectively, in a trial in which GZR was administered with PR. Transaminase elevations were of larger magnitude in the 400 and 800 mg dose groups and there was one clear case of liver injury in a patient who received 800 mg of GZR, but symptoms and laboratory abnormalities resolved after stopping the drug.

The transaminase elevations showed a characteristic pattern. After initial normalization of baseline transaminase abnormalities related to treatment of HCV infection, a rapid increase in transaminase levels from a treatment nadir occurred at or after Week 8 of treatment. The

applicant and FDA reviews refer to these laboratory findings as "late ALT/AST elevations;" however, with respect to a potential drug-related liver toxicity, I would not classify the transaminases as "late" and will thus refer to these abnormalities as GZR-associated transaminase elevations. To distinguish GZR-related elevations from background transaminase abnormalities related to HCV infection, DAVP and the applicant agreed on pre-specified definitions for conducting analyses of Phase 3 trials as detailed in the Clinical Review. Accordingly, GZR-related transaminase elevations in a pooled analysis of Phase 3 trials occurred in 12/1558 (0.8%) of patients receiving GZR vs. 0/105 patients receiving placebo (C-EDGE TN). All GZR-related transaminase elevations completely resolved by follow-up week 12 and most by follow-up Week 4. Symptoms potentially related to hepatic injury occurred in only 1 of the 12 subjects and consisted of abdominal pain two days after onset of transaminase increases. There were no grade 3 or 4 bilirubin elevations in these 12 subjects, but approximately half had Grade 1 total bilirubin elevations.

Higher transaminase elevation rates occurred in female, Asian, or older subjects as compared to male, White, or younger subjects, respectively. In population PK analyses using data from subjects who received the to-be marketed dose of 100 mg of GZR, GZR AUCs were estimated to be 30% higher in female subjects as compared to male subjects, 50% higher in Asian subjects as compared to White subjects, and 20% higher in older subjects (≥ 65 years old) as compared to younger subjects (< 65 years old). It is unclear to what extent the higher exposures contributed to the higher adverse event rates. Of note, cirrhotic subjects were not demonstrated to be at a higher risk of GZR-associated transaminase elevations than noncirrhotic subjects despite higher GZR exposures in cirrhotic subjects.

In a Phase 2 trial, one patient with Child-Pugh B cirrhosis (decompensated cirrhosis), for which EBR/GZR is contraindicated in the label for the FDC, had further liver decompensation resulting in death after receiving EBR 50mg and GZR 50mg. The event and death were attributed to the patient's underlying disease and not attributed to drug. This patient did not have characteristic transaminase elevations associated with GZR.

Merck commissioned an independent committee of drug-induced liver injury (DILI) experts and practicing HCV clinicians to assess the observed transaminases elevations and the overall hepatic safety profile of EBR/GZR. The committee concluded that no cases clearly fulfilled the accepted criteria for Hy's Law, although some patients met the numerical laboratory criteria. They stated that their overall level of concern regarding hepatic safety findings with EBR/GZR, administered at doses of 100mg/50mg is low. They recommended specific recommendations for transaminase (ALT) monitoring be provided in the label.

9. Advisory Committee Meeting

This application was not presented at an advisory committee because neither of the drugs in this FDC were first-in-class, efficacy was robust across multiple important subpopulations, and safety/tolerability issues were primarily limited to exposure-related transaminase elevations, events that can be readily monitored and managed. In addition, this product had breakthrough therapy designation for patients with CHC and ESRD and for GT4 infection. Generally products with BT designation are not taken to advisory committee so that reviews can occur

more efficiently. Also, by definition, a BT product has already been determined to have demonstrated promising clinical benefit for a population of unmet medical need.

10. Pediatrics

Merck submitted the required initial Pediatric Study Plan (iPSP) prior to the NDA submission. DAVP and the Pediatric Review Committee found the iPSP to be satisfactory with the addition of DAVP's recommendations.

Pediatric trials will be conducted as postmarketing requirements (PMR). For hepatitis C drug development adult trials precede pediatric development to identify optimal doses/exposures with respect to safety and efficacy before exposing children. Hepatitis C infection generally progresses over a period of years such that delays in the treatment of children are not considered risky. In addition children infected under the age of 3 years of age sometimes spontaneously clear infection, such that studies in ages 3 and younger are waived. The pediatric development plan includes a study in (b) (4) age (b) (4) ranging from 3- (b) (4) years.

11. Other Relevant Regulatory Issues

There were no significant issues related to clinical or manufacturing inspections. Six clinical sites inspected were for trials C-EDGE TN and C-EDGE TE.

There were no significant financial disclosure issues.

12. Labeling

The "label" or physician prescribing information is typically posted on-line with the Division Director's Summary Review shortly after product approval. Therefore this review will only address major issues that were resolved and discussed in earlier sections of this review.

- INDICATIONS AND USAGE section:
  The indication specifies that treatment is intended for patients with GT1 and 4 infections. (b) (4) A (b) (4) was considered for patients with certain baseline NS5A polymorphisms; however, DAVP did not consider the need to screen for baseline polymorphisms to be an absolute (b) (4) In clinical trials, overall response rates without screening approximated 95%. However, screening will help to guide choice of dosage regimen in a small percentage of patients who harbor NS5A polymorphisms and is better placed in Dosage and Administration section of the label in proximity to Dosage recommendations.

- DOSAGE AND ADMINISTRATION section:

The following statement will appear in the Dosage and Administration Section to recommend testing GT1a-infected patients for the presence of certain baseline NS5A polymorphisms prior to initiation of treatment to guide dosing recommendations:

Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance associated polymorphisms is recommended prior to initiation of treatment with ZEPATIER to determine the dosage regimen and duration [see Dosage and Administration (2.2)], Table 1. In subjects receiving ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93

The basis for choice of regimen and regimen duration have been discussed in this memorandum under the Clinical Efficacy Section

Dosage and Administration recommendations as they appear in the label are as follows:

Recommended Dosage Regimens and Durations for ZEPATIER for Treatment of HCV Genotype 1 or 4 in Patients with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + RBV‡	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a§ or 1b: PegIFN/RBV/PI-experienced¶	ZEPATIER + RBV‡	12 weeks
Genotype 4: Treatment-Naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + RBV‡	16 weeks

*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).
†NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. See section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV genotype 1a infected patients.
‡For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.
§The optimal ZEPATIER-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.
¶Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:

The label does not include a Boxed Warning, but as mentioned in the Clinical Pharmacology section of this memo, there are several drugs that are contraindicated for co-administration.

The major Warning of note is that which describes the potential for transaminase elevations occurring at approximately 8 weeks after initiation of therapy. Laboratory monitoring is

recommended at week 8 and additionally at week 12 (for those receiving a 16 week regimen).

The Warning is as follows:

> *5.1 Increased Risk of ALT Elevations*
> *During clinical trials with ZEPATIER with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]) [see Adverse Reactions (6.1)].*
>
> *Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.*

13. Post-marketing

This product does not require a REMS because the few identified safety issues can be satisfactorily addressed in the prescribing information as discussed previously.

Post-marketing Requirements (PMRs) and Post-marketing Commitments (PMCs)

The approval of EBR/GZR will trigger required pediatric studies under PREA. These PREA PMRs are:

1. A trial to evaluate the PK, safety and treatment response (using SVR(b) (4) of EBR/GZR in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection
2. A trial that collects long-term safety data for subjects enrolled in the pediatric EBR/GZR safety, PK and efficacy study. Data will be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of EBR and GZR including analyses of growth, sexual maturation and characterization of EBR and GZR resistance-associated substitutions in viral isolates from subjects failing therapy.

In order to characterize resistance to EBR/GZR and cross-resistance with other DAAs, a safety issue, the Agency has recommended the following PMRs under FDAAA:

3. Studies in HCV replicon systems that analyze site-directed mutant phenotypes carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a); studies will evaluate susceptibility to GZR and cross-resistance to other approved NS3/4A inhibitors.
4. Studies in HCV replicon systems that analyze site-directed mutant phenotypes carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a); studies will evaluate (b) (4) cross-resistance to other approved NS5A inhibitors

In the hope of establishing an optimal EBR/GZR-based treatment regimen for patients with baseline NS5A polymorphisms, the Division will issue a PMR for the following:

5. A clinical trial in HCV GT1a-infected subjects with baseline NS5A resistance-associated polymorphisms to evaluate if a longer duration of treatment with EBR/GZR and the addition of ribavirin reduce the rate of virologic relapse and viral resistance.

In addition, Merck has agreed to two PMCs:

1) to provide SVR24 data from the key efficacy trials of EBR/GZR
2) to evaluate the effect of the SLCO1B1 genotype on GRZ PK and response to EBR/GZR treatment in patients with CHC.

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/s/

JEFFREY S MURRAY
01/15/2016