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RESEARCH**

APPLICATION NUMBER:

208261Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 208261
Applicant Name	Merck Sharp & Dohme Corp.
Date of Submission	May 28, 2015
PDUFA Goal Date	January 28, 2016
Proprietary Name / Established (USAN) Name	Zepatier elbasvir and grazoprevir
Dosage Forms / Strength	tablets, 100mg/50mg
Applicant Proposed Indication(s)/Populations	ZEPATIER™ is indicated for the treatment of chronic hepatitis C virus (CHC) genotypes 1, 4, or 6 infection in adults.
Action:	Approval
Approved Indication(s)/Populations (if applicable)	ZEPATIER™ with or without ribavirin is indicated for the treatment of chronic hepatitis C virus (HCV) genotypes 1 or 4 infection in adults.

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer/Clinical Review	Sarita Boyd Prabha Viswanathan
Statistical Review	LaRee Tracy, Thamban Valappil, Dionne Price
Pharmacology Toxicology Review	Christopher Ellis, Hanan Ghantous, Abigail Jacobs
OPQ Review	Sharon Kelly, Monica Cooper, George Lunn, Ying Wang, Denise Digiulio, Jing Li, Florence Aisida, Stephen Miller, Jason Rodriguez, Paul Perdue, James Laurenson
Microbiology/Clinical Virology Review	Takashi Komatsu, Patrick Harrington, Jules O'Rear
Clinical Pharmacology Review	Su-Young Choi, Stanley Au, Luning Zhuang, Jeff Florian, and Shirley Seo
OSI	Antoine El-Hage, Susan Thompson, Kassa Ayalew
CDTL Review	Adam Sherwat
Deputy Division Director's Review	Jeff Murray

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

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 observed in the clinical trials safety database 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 of GZR in Phase 2 development (200 mg to 800 mg). 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. The product labeling includes a statement in the Warnings and Precautions section on increased risk of ALT elevations and recommendations for testing at baseline, week 8, and week 12 (if treatment will be given for 16 weeks).

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. 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 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	<ul style="list-style-type: none"> • 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. 	<p>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.</p>
Current Treatment Options	<ul style="list-style-type: none"> • 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 	<p>Because multiple treatment options are approved with high SVR rates and acceptable safety profiles, new products should not demonstrate a level of efficacy that would adversely impact the benefit risk ratio for the product. 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</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>available.</p> <ul style="list-style-type: none"> • There are currently no treatments approved for CHC in ESRD and patients on hemodialysis 	<p>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.</p>
Benefit	<ul style="list-style-type: none"> • 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 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 • Data were limited for GT4 patients who were TE with PR but data from GT1 TE patients help to support a dosage regimen recommendations. 	<p>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 mortality¹. The long term benefits, especially with respect to liver mortality, are substantial, especially considering the short duration of treatment (12-16 weeks).</p>
Risk	<ul style="list-style-type: none"> • 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 	<p>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. This adverse effect has been observed with other</p>

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>associated with GZR.</p> <ul style="list-style-type: none"> • It is unknown whether a subset of individuals with transaminase elevation could progress to more clinically significant liver toxicity but 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. 	<p>HCV NS3/4A protease inhibitors. 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.</p>
Risk Management	<ul style="list-style-type: none"> • 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 prior to starting therapy, 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. 	<p>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.</p>

2. Further discussion to support regulatory action

Background

Zepatier (elbasvir and grazoprevir) is a fixed dose combination tablet containing elbasvir, a hepatitis C virus NS5A inhibitor, and grazoprevir, a hepatitis C NS3/4A protease inhibitor that has been developed for the treatment of chronic hepatitis C (CHC) genotypes 1 and 4 used with or without ribavirin depending on virologic characteristics and treatment history. The applicant also requested an indication that included genotype 6 HCV, but (b) (4)

Zepatier received breakthrough therapy designation for the treatment of chronic HCV genotype 1 infection in patients with end stage renal disease on hemodialysis and for the treatment of chronic HCV genotype 4 infection. The application was also granted a priority review.

Chronic hepatitis C infection causes a significant burden of disease in the United States and globally. In the U.S. 3.2 million people are estimated to be infected with hepatitis C virus. New therapies to treat CHC offer the promise of important advances in the care of patients with CHC.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Zepatier. For a detailed discussion of NDA 208261, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Deputy Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

Product Quality

The Zepatier (elbasvir/grazoprevir) 50mg/100mg tablet is recommended for approval from a product quality standpoint. Based on the information from inspections, the manufacturing sites for the product are considered acceptable. The application is also found acceptable from the standpoint of biopharmaceutics and product quality microbiology for this solid oral dosage form.

Nonclinical Pharmacology/Toxicology

The recommendation from the pharmacology/toxicology reviewers is for approval. No specific target organs were identified in the nonclinical studies of elbasvir. In rat fertility studies a minor reduction in sperm count that was judged not to be a biologically significant finding. The main target organs of toxicity for grazoprevir were the liver and gallbladder in studies in dogs and mice. Liver related findings included increased liver size and weight,

increased ALT, AST, alkaline phosphatase (dogs) and total bilirubin. Other organs exhibiting toxicity in animal studies were found at exposures much higher than expected human exposures; the involved organs/tissues were testes (dogs), gastrointestinal tract (rats and mice), red blood cells (mice and dogs), and kidney (mice). Elbasvir and grazoprevir were not genotoxic in the battery of in vivo or in vitro assays that were performed.

Clinical Microbiology

The Clinical Virology Reviewer recommends that the data in NDA 208261 support approval. The review describes polymorphisms associated with reduced activity of NS5A inhibitors. In patients with HCV genotype 1a infection, the labeling recommends baseline testing for NS5A polymorphisms associated with resistance to determine the dosage regimen and duration. For patients with HCV genotype 1a and certain baseline polymorphisms, 16 weeks of treatment with the addition of ribavirin is recommended.

Clinical Pharmacology

The Clinical Pharmacology reviewers find the data in the application are acceptable and recommend approval for the application. Both grazoprevir and elbasvir are highly protein bound and metabolized by CYP3A4. The primary route of excretion of both drugs is in the feces with less than 1% of the dose excreted in the urine. Grazoprevir exposures were increased by 1.7 fold, 4.8 fold, and 11.7 fold in patients with mild, moderate and severe hepatic impairment, respectively. No dosage adjustment is recommended in patients with mild hepatic impairment. Zepatier is contraindicated in patients with moderate and severe hepatic impairment because of significant increases in exposures to grazoprevir; increased exposure to grazoprevir would increase the risk of exposure-related adverse effects including an increase in drug-related ALT elevations and risk of hepatic adverse effects. Dosage adjustment is not recommended for patients based on renal impairment as the renal clearance is only a very minor route of elimination. The labeling also includes information on drug interactions, drugs that are contraindicated with Zepatier, and drugs that require dosage adjustment or more frequent monitoring when administered with Zepatier.

Clinical/Statistical – Efficacy

Zepatier's efficacy was evaluated in five main clinical trials and shown to be efficacious in the treatment of chronic hepatitis C virus (CHC) infections in patients with genotype 1 and 4. The treatment duration and whether to add ribavirin to Zepatier is based on HCV genotype, history of prior treatment, and for patients with HCV genotype 1a, the presence of baseline NS5A polymorphisms. Two of the five clinical trials were placebo controlled, with placebo patients receiving treatment after the study was unblinded. The other three trials were historically controlled. Given the differences in response to treatment based on genotype, the data were analyzed by genotype. Response rates were generally higher than 90% for the different populations and HCV genotype categories analyzed. The Dosage and Administration

section of the product labeling describes treatment durations and whether to add ribavirin based on genotype, prior treatment history, and presence of baseline NS5A polymorphisms. Included among the trials is a trial that enrolled subjects with severe renal impairment including subjects on hemodialysis.

Safety

The safety database for Zepatier included over 1,700 subjects with chronic hepatitis C who received Zepatier for at least 12 weeks and 360 subjects who received at least 16 to 18 weeks. The most common side effects of Zepatier when administered without ribavirin were fatigue, headache and nausea. For treatment regimens that included the addition of ribavirin to Zepatier, the most common side effects of moderate or greater severity were anemia and headache. Approximately 1% of patients experienced increases in ALT to 5 times the upper limit of normal. These elevations were usually asymptomatic and occurred at or after week 8 of treatment. The product labeling includes a statement in the Warnings and Precautions section of the labeling noting the increased risk of ALT increases, and recommends testing of liver-related analytes at baseline, week 8, and week 12 (if treatment will continue for 16 weeks). The warning also notes circumstances under which discontinuing Zepatier therapy should be considered and signs and symptoms of more serious liver adverse effects that patients should be aware of and if present, should prompt patients to call to the attention of their healthcare provider.

Advisory Committee Meeting

The application for Zepatier (elbasvir/grazoprevir) was not referred to an FDA Advisory Committee because this drug is not the first in its class, and its safety profile is similar to that of other drugs approved for this indication.

Pediatrics

Pediatric studies are being waived for ages birth to less than three years because the necessary studies are impossible or highly impracticable. This is because in this age group there is a high rate of spontaneous viral clearance and disease progression is slow for children who develop chronic infection.

Pediatric studies for ages three years to less than 18 years are being deferred for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The approval letter contains the pediatric studies that are required for ages three years to less than 18 years.

Labeling

The sponsor requested product labeling for genotypes 1, 4

(b) (4)

(b) (4)

In addition, based on review of the data on baseline NS5A polymorphisms, a recommendation for testing for baseline polymorphisms in patients with genotype 1a was added to the product labeling and the dosage regimen and durations were changed to provide dosing recommendations that take the test results into consideration. The product labeling also contains a statement in Warnings and Precautions about increased risk of ALT elevations and contraindications for use of Zepatier in patients with moderate and severe hepatic impairment.

Risk Evaluation and Mitigation Strategies (REMS)

This application does not include a REMS. The product labeling including the package insert and patient package insert provides adequate information on the product, its risk and benefits, and recommendations on how to mitigate risks of adverse effects.

Postmarketing Requirements and Commitments

In addition to the required Pediatric studies, there are also postmarketing requirements to further evaluate mutations associated with resistance in nonclinical studies and baseline polymorphisms in a clinical trial (for subjects with genotype 1a HCV). There are also postmarketing commitments for a pharmacokinetic study and reporting SVR24 data for three clinical trials.

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/s/

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01/28/2016