Compositions and Methods for Treating Hepatitis C Virus

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 61/564,500, filed November 29, 2011, and 61/707,459, filed September 28, 2012, and claims the benefit under 35 U.S.C. § 120 of International Application No. PCT/US2012/055621, filed September 14, 2012, and U.S. Application No. 13/661,509, filed October 26, 2012, all of which are incorporated by reference in their entireties.

Field of the Invention

Disclosed herein are a composition and unit dosage form for the treatment of hepatitis C virus (HCV) infection comprising GS-7977 and at least one pharmaceutically acceptable excipient, as well as methods for making the said composition and unit dosage form. Also disclosed herein is a method of treating a subject, preferably a human, infected with hepatitis C virus, said method comprising administering to the subject for a time period an effective amount of GS-7977 and an effective amount of ribavirin. In one aspect, the method comprises administering to the subject an interferon-free treatment regimen comprising an effective amount of GS-7977 and an effective amount of ribavirin. In a particular aspect, the method is sufficient to produce an undetectable amount of HCV RNA in the subject for at least 12 weeks after the end of the time period.

Background

Hepatitis C virus ("HCV") infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated by the World Health Organization to be about 3% of the world's population. (World Health Organization, Hepatitis C (2002).) According to the U.S. Centers for Disease Control and Prevention, HCV is the most common blood-borne infection in the United States, with an estimated 3.2 million people (1.8%) chronically infected in the United States alone. (U.S. Centers for Disease Control and Prevention, Viral Hepatitis Surveillance – United States, 2010; U.S. Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report 70(17): 537-539

(May 6, 2011).) An estimated 150-180 million individuals are chronically infected with HCV worldwide, with 3 to 4 million people infected each year. (World Health Organization, Hepatitis C, Fact Sheet No. 164 (July 2012); Ghany et al., Hepatology (2009) 49(4): 1335-1374.) Once infected, about 20% of people clear the virus, but the rest can harbor HCV for the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. (Naggie et al., J. Antimicrob. Chemother. (2010) 65: 2063-2069.) The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring.

The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural ("NS") proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase, from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex. (K. Ishi, et al, Hepatology (1999) 29: 1227-1235; V. Lohmann, et al., Virology (1998) 249: 108-118.) Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

A number of potential molecular targets for drug development of direct acting antivirals as anti-HCV therapeutics have now been identified including, but not limited to, the NS2-NS3 autoprotease, the N3 protease, the N3 helicase, and the NS5B polymerase. The RNA-dependent RNA polymerase is essential for replication of the single-stranded, positive sense, RNA genome, and this enzyme has elicited significant interest among medicinal chemists. Another auxiliary protein of HCV is referred to as NS5A. The NS5A nonstructural protein is a phosphoprotein, with no apparent enzymatic

activity; however it acts as a multifunctional regulator of cellular pathways, including host cell growth, immunity and innate immunity, and virus replication. (Appel et al., J. Virol. (2005) 79: 3187-3194; Evans et al., Proc. Natl. Acad. Sci. USA (2004) 101: 13038-13043; Gale et al., Nature (2005) 436: 939-945; Gale et al., Virology (1997) 230: 217-227; Ghosh et al., J. Gen. Virol. (1999) 80(Pt 5): 1179-1183; Neddermann et al., J. Virol. (1999) 73: 9984-9991; Polyak et al., Hepatology (1999) 29: 1262-1271; Shimakami et al., J. Virol. (2004) 78: 2738-2748; Shirota et al., J. Biol. Chem. (2002) 277: 11149-11155; and Tan et al., Proc. Natl. Acad. Sci. U. S. A. (1999) 96: 5533-5538.) NS5A is associated with host cell membranes through its N-terminal amphipathic helix, where it is a part of the replication complex. (Elazar et al., J. Virol. (2004) 78: 11393-11400 and Penin et al., J. Biol. Chem. (2004) 279: 40835-40843.) Recent studies suggest that NS5A is organized into three domains: the first 213 amino acids in the N-terminal domain constitutes domain I and contains a zinc binding motif suggesting that the protein is a zinc metalloprotein and domains II and III are in the C-terminal region of the protein. (Tellinghuisen et al., J. Biol. Chem. (2004) 279: 48576-48587 and Tellinghuisen et al., Nature (2005) 435: 374-379.) NS5A exists in two phosphorylated forms: a basal form of 56 kD and a hyperphosphorylated form of 58 kD. The protein is phosphorylated at specific sites, primarily on serine residue within domains II and III, by host cell kinases. (Ide et al., Gene (1997) 201: 151-158; Kaneko et al., Biochem. Biophys. Res. Commun. (1994) 205: 320-326; Katze et al., Virology (2000) 278: 501-513; Reed et al., J. Biol. Chem. (1999) 274: 28011-28018; Reed et al., J. Virol. (1997) 71: 7187-7197; and Tanji et al., J. Virol. (1995) 69: 3980-3986.)

The initially-approved standard of care ("SOC") for the treatment of chronic HCV infection is a combination therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b (collectively "peginterferon" or "PEG") used alone or in combination with ribavirin ("RBV"). The primary goal of treatment for chronic hepatitis C is a sustained virologic response ("SVR"), which refers to an undetectable level of serum HCV RNA maintained for a period of time post-treatment. Host factors including age, body weight, race, and advanced fibrosis influence the outcome of treatment (Dienstag and McHutchison Gastroenterology (2006)130: 231-264 and Missiha et al.,

Gastroenterology (2008) 134: 1699-1714), but are poor predictors of response. In contrast, viral factors like the genotype and the on-treatment pattern of viral response can be used to determine the likelihood of treatment success and guide treatment duration individually, and they have proven to be very useful in clinical practice. (Ge et al., Nature (2009) 461: 399-401.)

In spite of an encouraging response in some patients to SOC treatment, the overall response to peginterferon/ribavirin combination therapy among patients infected with Hepatitis C virus is only about 50%. SVR rates are <50% for patients infected with genotype 1 HCV treated with a prolonged duration (48-72 weeks) of peginterferon/ribavirin therapy. (Naggie et al., J. Antimicrob. Chemother. (2010) 65: 2063-2069.) Accordingly, there is a need to provide a therapy resulting in improved SVR compared to the outcome of treatment with peginterferon alone or in combination with ribavirin. There is also a need to provide a therapy that reduces the time in which patients show evidence of complete viral suppression (negative HCV status) following the initiation of treatment.

Peginterferon alfa-2a ("PEG-IFN-α-2a" or "peginterferon α-2a"), marketed under the trademark PEGASYS®, is an antiviral administered by subcutaneous injection indicated for, among other things, treatment of chronic hepatitis C ("CHC") when administered alone or in combination with ribavirin. PEGASYS® is indicated for the treatment of CHC in patients with compensated liver disease not previously treated with interferon alpha, in patients with histological evidence of cirrhosis and compensated liver disease, and in adults with CHC/HIV co-infection. Combination therapy using PEG-IFN-α-2a and ribavirin is recommended unless the patient has contraindication to or significant intolerance to ribavirin.

Peginterferon alfa-2b ("PEG-IFN-α-2b" or "peginterferon α-2b"), marketed under the trademark PEGINTRON®, is also administered by subcutaneous injection and is indicated for use alone or in combination with ribavirin to treat CHC in patients with compensated liver disease. Like PEG-IFN-α-2a, PEG-IFN-α-2b has undesirable side effects.

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Ribavirin ("RBV"), marketed under the trademark COPEGUS®, is a nucleoside analogue indicated for the treatment of CHC virus infection in combination with peginterferon in patients 5 years of age and older with compensated liver disease not previously treated with peginterferon, and in adult CHC patients co-infected with HIV. Ribavirin alone is not approved for the treatment of CHC. (COPEGUS® FDA-approved label, revised 08/2011.) Clinical trials have shown that ribavirin alone can normalize alanine aminotransferase ("ALT") levels transiently during the course of treatment in some patients with CHC infections. However, these studies have reported that ribavirin alone did not reduce HCV RNA levels during or after therapy and did not produce any sustained virologic response. (Di Bisceglie et al., Ann. Intern. Med. (1995) 123(12): 897-903; Dusheiko et al., J. Hepatology (1996) 25: 591-598; Bodenheimer, Jr., et al., Hepatology (1997) 26(2): 473-477.) One clinical study reported observing a decrease in HCV RNA from treatment with ribavirin monotherapy (1.0 to 1.2 g daily for 24 weeks); however, the observed HCV RNA decrease was transient and no patient receiving ribavirin monotherapy cleared HCV RNA. (Pawlotsky et al., Gastroenterology (2004) 126: 703-714.)

Treatment of CHC using peginterferon alone or in combination with ribavirin has several disadvantages. First and foremost, this therapy is not effective for many patients. For instance, certain Phase 3 clinical trials using the combination of peginterferon and ribavirin reported SVR rates of 54 to 63%, but additional studies show that the SVR rates may be much lower in certain populations. (Feurstadt et al., Hepatology (2010) 51(4): 1137-1143.) Second, use of peginterferon and ribavirin is associated with certain adverse events. For instance, the boxed warning on the PEGASYS® label states that use of peginterferon may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. (PEGASYS® (peginterferon alfa-2a) FDA-approved label, revised 09/2011.) Additionally, the boxed warning on the COPEGUS® label states that ribavirin adverse effects may include hemolytic anemia and that significant "teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin." (COPEGUS® (ribavirin) FDA-approved label, revised 08/2011.) Finally, the peginterferon/ribavirin treatment protocol is quite expensive.

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