CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Technivie™

GENERIC NAME
Ombitasvir/paritaprevir/ritonavir

MANUFACTURER
AbbVie, Inc.

DATE OF APPROVAL
February 27, 2017

PRODUCT LAUNCH DATE
Already available on the market

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)

Current Indication(s)
Indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis

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New Indication(s)
Indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection with compensated cirrhosis

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY

The AGATE I trial assessed Technivie plus ribavirin (RBV) in patients with HCV genotype 4 infection and compensated cirrhosis. Eligible patients included those age 18 years or older with chronic HCV genotype 4 infection and compensated cirrhosis. Exclusion criteria included a HBV or HIV screening test, hepatic decompensation, and previous HCV treatment with direct acting antivirals.The trial utilized a global multicenter, open-label design in which 120 HCV genotype 4 infected adults with compensated cirrhosis were randomized to 12 (n=59) or 16 weeks (n=61) of Technivie plus RBV treatment. Subjects were stratified by treatment status (treatment-naïve or pegIFN/RBV treatment-experienced) and type of non-response (no response, partial response, relapse).

Of the 59 subjects in the 12 week arm, median age was 56 years (range: 43 to 81); 51% were treatment-naïve, 29% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 12% were prior pegIFN/RBV relapsers; 76% were male; 17% were Black; 29% had a body mass index of at least 30 kg/m2; 76% had baseline HCV RNA levels of at least 800,000 IU per mL; 86% had IL28B (rs12979860) non-CC genotype; 12% had platelet counts of less than 90 x 109 per L; and 5% had albumin less than 3.5 mg per dL.

The primary outcome was proportion (% [n/N]) of patients with a sustained viral response (HCV RNA <25 IU/mL) at post-treatment week 12 (SVR12) in the intention to treat population with the lower end of the 97.5% confidence interval compared with a clinically relevant threshold of 67% (based on historical pegIFN/RBV SVRs) to achieve superiority.

Secondary outcomes included proportion of patients with virological failure as well as an SVR12 comparison between the 12 and 16 week treatment groups. A safety analysis included all patients who received at least one dose of study drug and extended to 30 days post treatment.

Based on an SVR12 rate of 67% established as a superiority threshold from pegIFN/RBV historical data, the study demonstrated superiority given that the lower ends of the 97.5% CI set for both the 12 and 16 week treatment groups exceeded 67%. Table 1 presents the SVR12 rates for HCV genotype 4 infected subjects with compensated cirrhosis treated with Technivie plus RBV for 12 and 16 weeks. Treatment over 16 weeks was not shown to increase SVR12 rates in comparison with treatment for 12 weeks so it is not labeled for the new indication. The two incomplete trials in the 12 week group represent noncompliance and virological breakthrough; the one incomplete trial in the 16 week group represents a missed follow-up appointment due to administrative error. There were no relapses. The safety analysis showed the regimen was well

tolerated with most adverse events reported as mild in severity and with no discontinuations due to adverse events.

Table 1. AGATE-I Trial:

SVR12 for HCV Genotype 4-Infected Subjects with Compensated Cirrhosis

Treatment outcome	**Technivie with RBV**
SVR12 (% [n/N], CI) in 12 week group	97% (57/59), CI 86.7-99.2
SVR12 (% [n/N], CI) in 16 week group	98% (60/61), CI 89.6-99.8
Outcome for subjects without SVR12	**12 week group**
On-treatment VF[a]	2% (1/59)
Relapse[b]	0 (0/57)
Other[c]	2% (1/59)

a. "On-treatment virologic failure (VF)" was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed increase from nadir in HCV RNA > 1 log10 IU/mL during treatment, or HCV RNA ≥ 25 IU/mL persistently during treatment with at least 6 weeks of treatment.

b. "Relapse" was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA less than 25 IU/mL at last observation during at least 11 weeks of treatment.

c. "Other" includes subjects not achieving SVR12 but not experiencing on-treatment virologic failure or relapse (in this case the subject was lost to follow-up after the first visit).

The regimen for both of Technivie's indications is 2 tablets PO once daily, equaling a total dose of paritaprevir (150mg), ritonavir (100mg), ombitasvir (25mg), plus weight-based RBV for 12 weeks.

CONTRAINDICATIONS
The contraindications to ribavirin also apply to this combination regimen

BLACK BOX WARNINGS
Hepatitis B virus (HBV) reactivation in patients co-infected with HCV and HBV

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DRUG INTERACTIONS
Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir and ritonavir are inhibitors of BCRP and P-gp. Ritonavir is an inhibitor of CYP3A4. Co-administration of Technivie with drugs that are substrates of CYP3A, P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

ADVERSE REACTIONS
The most commonly reported adverse reactions (incidence greater than 10% of subjects, all grades) observed with treatment with Technivie with ribavirin for 12 weeks in patients without cirrhosis were asthenia, fatigue, nausea and insomnia.

The most common adverse events (incidence greater than 10% of subjects, all grades) observed with treatment with Technivie and ribavirin for 12 weeks in patients in compensated cirrhosis were fatigue, asthenia, headache, musculoskeletal pain, pruritus, insomnia/sleep disorder, skin reactions, mood disorders, nausea, dizziness and dyspnea.

DOSAGE AND ADMINISTRATION
Two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content in combination with weight-based RBV for 12 weeks.

PRODUCT AVAILABILITY
Tablets: Ombitasvir (12.5mg)/paritaprevir (75mg)/ritonavir (50mg)

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Sofosbuvir (400mg)/valpatasvir (100mg) (Epclusa)	One tablet PO QD for 12 weeks	
Elbasvir (50mg)/grazoprevir (100mg) (Zepatier)	One tablet PO QD for 12 weeks	
Ledipasvir (90mg)/sofosbuvir (400mg) (Harvoni)	One tablet PO QD for 12 weeks	

Boldface indicates generic availability

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Utilization Management Recommendation
There is significant potential for inappropriate use and utilization management should be considered for the following reasons: • An opportunity exists to obtain significant laboratory and clinical information necessary to determine appropriate use of the medication – specifically, confirmation of HCV genotype 4 infection as well as cirrhosis status and treatment history. • An opportunity exists to assure that the appropriate combination regimen and treatment duration are prescribed. Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
Based on AASLD-IDSA guidelines it would be clinically appropriate to provide equal access to any of the following four FDA labeled drugs or to prefer any one drug over another: • Technivie, Epclusa, Zepatier, Harvoni. AASLD-IDSA guidelines recommend against using FDA labeled drugs Sovaldi and Olysio based on the following rationales: • Solvaldi and Olysio regimens include interferon which is associated with higher rates of serious adverse events, longer treatment durations, higher pill burdens, numerous drug interactions, frequent dosing, and higher intensity of safety and efficacy monitoring. • Sovaldi and Olysio have demonstrated inferior results when compared to current, shorter, well-tolerated regimens that not only consist of combinations of direct-acting antiviral drugs but do not include interferon-based regimens. For these reasons it would not be appropriate to prefer Sovaldi or Olysio over any of the four recommended drugs listed above.

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