ヴィキラックス配合錠
に関する資料

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1.5 起原又は発見の経緯及び開発の経緯

1.5.1 起原又は発見の経緯

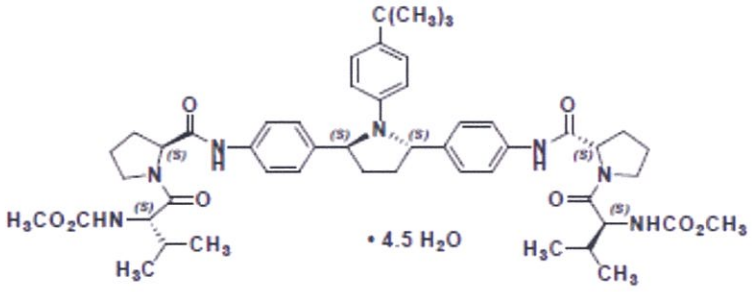
オムビタスビル水和物（以下「OBV」）は C 型肝炎ウイルス（以下「HCV」）非構造たん白質 5A（以下「NS5A」）の阻害剤であり，パリタプレビル水和物（以下「PTV」）は HCV 非構造たん白質 3/4A（以下「NS3/4A」）プロテアーゼ阻害剤である。ヴィキラックス錠は，インターフェロン（以下「IFN」）を使用しない経口投与の C 型慢性肝炎治療薬として開発した OBV，PTV 及び薬物動態学的エンハンサーであるリトナビルの配合剤である。

(1) OBV

OBV は HCV NS5A 阻害剤で，ジェノタイプ 1a，1b，2a，2b，3a，4a，5a 及び 6a サブジェノミックレプリコン細胞の複製をそれぞれ 14，5.0，12，4.3，19，1.7，3.2 及び 366 pmol/L（50%有効濃度［以下「EC_{50}値」］）の濃度で阻害する。

OBV の構造式を図 1.5-1 に示す。

図 1.5-1. OBV 構造式

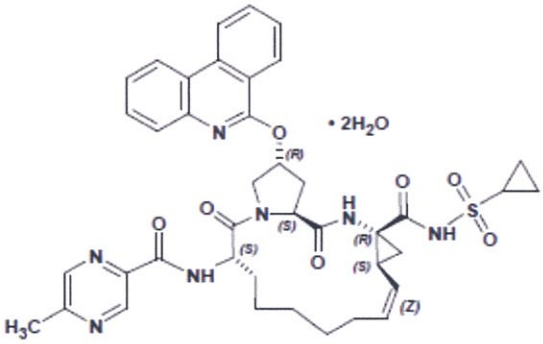


(2) PTV

PTV は，HCV NS3/4A プロテアーゼ阻害剤で，ジェノタイプ 1a，1b，2a，2b，3a，4a 及び 6a サブジェノミックレプリコン細胞の複製をそれぞれ 1.0，0.21，9.8，107，19，0.09 及び 0.68 nmol/L（EC_{50} 値）の濃度で阻害する。PTV は主としてチトクロム P450 3A4（以下「CYP3A4」）により代謝される。許容できる投与頻度で有効な曝露量を得るために，PTV は CYP3A4 の強力な阻害剤であるリトナビルと併用される。

PTV の構造式を図 1.5-2 に示す。

図 1.5-2. PTV 構造式



(3) OBV/PTV/r 配合剤

本邦では，HCV 感染患者の約 70%がジェノタイプ 1 に感染し，その他の HCV 感染患者はジェノタイプ 2 に感染していることから，本邦での開発は OBV 及び PTV/r の直接作用型抗ウイルス薬（以下「DAA」）2 剤による治療法を選択した。本邦では HCV ジェノタイプ 1 及びジェノタイプ 2 の占める割合が高いこと，またこれらの HCV ジェノタイプに対して本 DAA 2 剤は高い抗ウイルス活性を示すことから，本邦における HCV ジェノタイプ 1 及びジェノタイプ 2 に対する治療は OBV 及び PTV/r の DAA 2 剤併用による開発を行うこととした。

本邦において，DAA 2 剤を配合した OBV/PTV/r 25/150/100 mg の 1 日 1 回 12 週間投与は，ジェノタイプ 1 型 C 型慢性肝炎に対して 2015 年 9 月に承認された。今回，ジェノタイプ 2 型 C 型慢性肝炎に対して，ジェノタイプ 1 型 C 型慢性肝炎と同じ DAA 2 剤とリバビリン（以下「RBV」）の 16 週間併用投与での効能追加の申請を行うこととした。

OBV 及び PTV/r の併用投与は，HCV に対して異なる作用機序を持ち，耐性プロファイルが異なることから，それぞれの薬剤に対して治療抵抗性を生じる耐性変異による治療不成功例を軽減させることが期待される。本剤は固定用量配合剤として使用されること，またリトナビルとの併用により高い曝露量が得られることから，OBV，PTV 及びリトナビルを 1 日 1 回投与の配合剤とすることは，単剤の場合での併用服薬不遵守などによる曝露量の減少で引き起こされるウイルス耐性変異の出現リスクを抑制することが期待される。

1.5.2 本剤の対象疾患及び臨床上の位置づけ

1.5.2.1 C 型慢性肝炎の概要

C 型慢性肝炎は，公衆衛生上の問題となっており，その感染者数は，本邦では 150–200 万人と推定されている [1]。C 型慢性肝炎は，本邦では 1930 年代及び 1940 年代に拡大し，C 型慢性肝炎患者は欧米に比べて高齢であることから，今後数年から数十年で C 型慢性肝炎の健康保険負担が増大すると予測されている。HCV 感染後，約 70%の患者で HCV 感染が持続し，慢性肝炎へ

と移行する[1]。C 型慢性肝炎患者では，ウイルスの自然排除は年率 0.2%と稀であり，HCV 感染による炎症の持続により肝線維化が惹起され，肝硬変や肝細胞癌へと進展する[2]。肝硬変は，C 型慢性肝炎患者の約 20%に認められる[3]。肝硬変を伴う合併症には肝代償不全があり，腹水，脳症，静脈瘤出血，肝腎症候群又は肝合成機能障害などが生じる。また，肝細胞癌は 1 年あたり約 3%の患者に発症する[4-7]。肝移植を行わない場合，非代償性肝硬変患者の約半数が 5 年以内に死に至る[8]。HCV 感染及び HCV 感染から続発した合併症の有病率が高いため，HCV 感染は肝細胞癌の発生率上昇の主な要因になっており[9]，発展途上国では肝移植の適応疾患となっている[10,11]。肝硬変が代償性であり，持続性ウイルス学的著効（以下「SVR」）が認められ，非代償化する危険性を本質的に取り除かれた患者では，組織学的な寛解がもたらされ，肝細胞癌に至る危険性を 1/3 に軽減することができる[12-14]。

HCV は，7 種の主なジェノタイプ（ジェノタイプ 1 からジェノタイプ 7）に分類され，さらに異なるサブタイプに分けられる[15]。本邦においては HCV 感染患者の約 70%がジェノタイプ 1 に，又その他の患者はジェノタイプ 2 に感染している[16,17]。

1.5.2.2 C 型慢性肝炎の治療の現状

C 型慢性肝炎治療の目標は，HCV 持続感染によって惹起される慢性肝疾患の長期予後の改善，即ち，肝癌並びに肝疾患関連死を抑止することにある。そのための効果的な治療として，ウイルス排除が重要と考えられており，高齢者や肝硬変を含む高発癌リスク群では，早期に抗ウイルス療法が考慮されるべきとされている[1]。

本邦では，1992 年に IFN 製剤が C 型慢性肝炎治療薬として承認され，その後 IFN と RBV との併用療法やペグインターフェロン（以下「pegIFN」）と RBV との併用療法が開発され，ジェノタイプ型に応じて投与期間が最適化された。日本人における未治療のジェノタイプ 2 型 C 型慢性肝炎患者において，IFN 製剤を 24 週間投与した時の SVR 達成率は 64%–82%[18-20]，前治療不成功患者に IFN 製剤を再投与した時の SVR 達成率は約 40%と報告されている[18]。また，最近の研究では，IFN 製剤に対する反応性は HCV ジェノタイプ 2a とジェノタイプ 2b で差があり，ジェノタイプ 2b 感染患者に比べてジェノタイプ 2a 感染患者で高い SVR 達成率を示すことが示唆されている[18-20]。この反応性の差は，投与開始前のウイルス量及び宿主のインターロイキン 28B 遺伝子多型と関連する可能性が報告されている[18-20]。

IFN 又は pegIFN と RBV の併用投与では，発熱，悪寒，倦怠感，嘔気，食欲不振，白血球減少，好中球減少，血小板減少，ヘモグロビン減少など[21]，それらの多くは IFN に起因する副作用が認められている。IFN 製剤による治療では，SVR 達成率が低く副作用が認められるため，有効性が高く IFN を使用しない治療法の開発が進められてきた。

2014 年に HCV NS3/4A プロテアーゼ阻害作用を有する DAA のテラプレビル，pegIFN 及び RBV の 24 週間併用療法が本邦で承認され，ジェノタイプ 2 型 C 型慢性肝炎に対する SVR 達成率は改善し，前治療再燃患者における SVR24 達成率は 88%に向上した。しかし，前治療無効患者におけるテラプレビル，pegIFN 及び RBV の 3 剤併用療法の SVR24 達成率は 50%であり，治療効果は不十分であった[22]。また，この 3 剤併用療法では，pegIFN 及び RBV による副作用に加

えて，中毒性表皮壊死融解症や皮膚粘膜眼症候群（スティーブンス・ジョンソン症候群）を含む重度の皮膚障害の発現リスクが増大し，更に pegIFN 及び RBV の 2 剤併用療法に比べて貧血の悪化が強く，既存の腎疾患を悪化させることが知られている。なお，テラプレビル，pegIFN 及び RBV の 3 剤併用療法は，代償性肝硬変患者に対する適応はジェノタイプにかかわらず得られていない。

2015 年に核酸アナログのポリメラーゼ阻害剤であるソホスブビルと RBV の併用療法が，代償性肝硬変を含むジェノタイプ 2 型 C 型慢性肝炎患者におけるウイルス血症の改善の適応に対して本邦で承認された。ソホスブビルと RBV の 12 週間併用療法における SVR12 達成率は 97%を示し，特に代償性肝硬変患者における SVR12 達成率は 94%を示した。この 2 剤併用療法の忍容性は良好であり，投与中止に至った患者は認められなかった。ソホスブビルと RBV 併用の第 III 相試験で報告された主な有害事象は，鼻咽頭炎，貧血，頭痛であった[23]。

以上のように，本邦におけるジェノタイプ 2 型 C 型慢性肝炎患者の治療においては，安全で有効性が高く，簡便で，経口投与が可能な IFN を使用しない新たな治療法が求められている。

1.5.3 開発の経緯

本剤の開発経緯を表 1.5-1 に示す。

表 1.5-1. 開発の経緯

試験番号			実施期間	2009	2010	2011	2012	2013	2014	2015
国内	第 III 相試験	M14-153 (GIFT-2)	2014 年 1 月 14 日 - 2015 年 4 月 7 日						1	4
	第 III 相試験	M13-004 (GIFT-1)	2013 年 12 月 25 日 - 2014 年 10 月 17 日					12	10	
	第 II 相試験	M12-536	2012 年 7 月 24 日 - 2014 年 5 月 14 日				7		5	
	第 I 相試験	M[redacted]-384	20[redacted] 年 [redacted] 月 [redacted] 日 - 20[redacted] 年 [redacted] 月 [redacted] 日		[redacted]					
	第 I 相試験	M[redacted]-771	20[redacted] 年 [redacted] 月 [redacted] 日 - 20[redacted] 年 [redacted] 月 [redacted] 日						[redacted]	
	第 I 相試験	M[redacted]-247	20[redacted] 年 [redacted] 月 [redacted] 日 - 20[redacted] 年 [redacted] 月 [redacted] 日						[redacted]	
国外	効果を裏付ける試験		20[redacted] 年 [redacted] 月～20[redacted] 年 [redacted] 月	[redacted]						[redacted]

1.5.3.1 非臨床試験の概略

OBV/PTV/r 配合錠は，セログループ 1（ジェノタイプ 1）の C 型慢性肝炎又は C 型代償性肝硬変におけるウイルス血症の改善を効能・効果として 2015 年 2 月に承認申請し，2015 年 9 月に承認された。主要な非臨床試験成績は初回承認申請時に提出済みであり，今回の効能追加申請では，セログループ 2（ジェノタイプ 2）に対する効果を裏付ける提出済みの薬効薬理試験及び追加実施した薬理試験の成績を要約した。

1.5.3.2 薬理学試験の概要

OBV は，HCV 複製に必須な HCV NS5A の阻害剤である。PTV は，HCV 遺伝子にコードされる複合たん白質のプロセシング及び HCV 複製に必須な HCV NS3/4A プロテアーゼの阻害剤である。また，リトナビルは，PTV の血漿中濃度を上昇させる。

HCV レプリコン細胞において，OBV は HCV 複製を阻害し，ジェノタイプ 2a 及び 2b に対する EC_{50} 値はほぼ同等であったのに対し，PTV は，ジェノタイプ 2a に比較してジェノタイプ 2b に対する抗 HCV 活性は 11 倍低下した。PTV に対する耐性を示す NS3 の主要な変異は，ジェノタイプ 2a 及び 2b ともに D168 であった。OBV に対する耐性を示した NS5A の主要な変異は，ジェノタイプ 2a では T24A/S 及び F28C/S であり，ジェノタイプ 2b では，L28F，L/M31I/V 及び C92S/Y であった。

1.5.3.3 臨床開発の概略

1.5.3.3.1 第 I 相試験

本邦での初回申請以降，外国人健康被験者を対象とした DAA 2 剤（OBV/PTV/r 25/150/100 mg）及び/又は DAA 3 剤（OBV/PTV/r 25/150/100 mg + dasabuvir 250 mg）について，以下の薬物相互作用試験（5 試験）を行った。

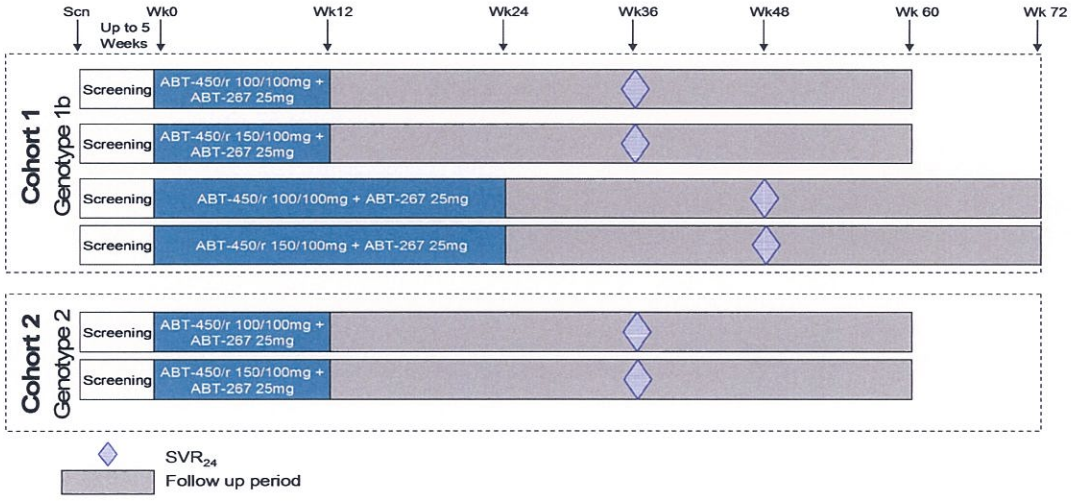
- 一般的に併用される薬剤との薬物相互作用試験（3 試験：M[redacted]-230 試験，M[redacted]-197 試験，M[redacted]-012 試験）
- ヒト免疫不全ウイルス治療薬との薬物相互作用試験（1 試験：M[redacted]-228 試験）
- ソホスブビルとの薬物相互作用試験（1 試験：M[redacted]-527 試験）

1.5.3.3.2 国内第 II 相試験

M12-536 試験は，日本人 HCV ジェノタイプ 1b 又はジェノタイプ 2 感染患者を対象に，OBV 及び PTV/r を投与した時の安全性，忍容性，抗ウイルス活性及び薬物動態を評価する第 II 相，無作為化，並行群間，用量設定，非盲検試験であり，国内 18 施設で実施した。HCV ジェノタイプ 1b 感染被験者（コホート 1）には，OBV（25 mg 1 日 1 回）と PTV/r（100/100 mg 1 日 1 回又は 150/100 mg 1 日 1 回）を 12 週間又は 24 週間投与し，HCV ジェノタイプ 2 感染被験者（コホート 2）には，OBV（25 mg 1 日 1 回）と PTV/r（100/100 mg 1 日 1 回又は 150/100 mg 1 日 1 回）

を 12 週間投与した。対象被験者は全て pegIFN 及び RBV の前治療歴があり，肝硬変の認められない被験者であった。本項では，国内第 III 相試験における用法・用量の選択を裏付ける HCV ジェノタイプ 2 感染被験者に関する有効性データのみを示す。本試験のデザインを図 1.5-3 に示す。

図 1.5-3. M12 536 試験のデザイン



ABT-450 = PTV; ABT-267 = OBV

本試験の主要目的は，OBV 25 mg と PTV/r 150/100 mg の 1 日 1 回及び OBV 25 mg と PTV/r 100/100 mg の 1 日 1 回を HCV ジェノタイプ 1b 感染被験者には 12 週間又は 24 週間，また HCV ジェノタイプ 2 感染被験者には 12 週間投与した時の安全性及び抗ウイルス活性（SVR24 達成率）を評価することであった。

HCV ジェノタイプ 2 感染被験者において，SVR12 達成率は PTV 100 mg 投与群に比べて PTV 150 mg 投与群で高かった（PTV 150 mg 投与群：72.2%［13/18 名］；95%信頼区間：46.52%–90.31%，PTV 100 mg 投与群：57.9%［11/19 名］；95%信頼区間：33.50%–79.75%）（M12–536 試験 CSR Table 12 及び Table 13）。また，OBV と PTV/r の併用投与時の安全性及び忍容性は良好であった。

国内第 II 相試験（M12-536 試験）で得られた成績，HCV ジェノタイプ 2 感染被験者を対象とした海外第 IIa 相試験（M12-998 試験）において SVR 達成率は OBV 及び PTV/r と RBV の併用投与で改善したこと [24]（2.5.1.3.4 項参照），さらに曝露－反応モデル及びシミュレーションの結果より，HCV ジェノタイプ 2 感染患者に対する OBV/PTV/r と RBV の投与期間は 12 週間から 16 週間が適切であることが示唆された。そこで，国内第 III 相試験では OBV/PTV/r 配合錠を用いて OBV/PTV/r 25/150/100 mg と RBV を 12 週間又は 16 週間併用投与し，HCV ジェノタイプ 2

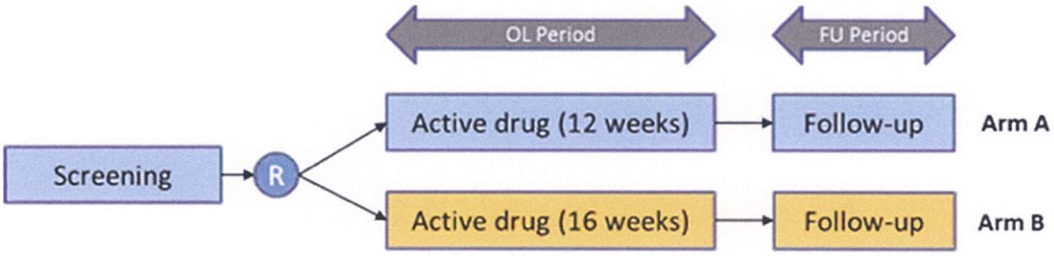
感染患者における耐性関連変異の出現リスクを抑制して SVR 達成率を最大化するための適切な投与期間を検討することとした。

1.5.3.3.3 国内第 III 相試験

1.5.3.3.3.1 M14-153 試験

M14-153 試験（GIFT-2）は，未治療及び IFN 既治療（代償性肝硬変を含む）の HCV ジェノタイプ 2 感染患者を対象として，OBV/PTV/r 25/150/100 mg と RBV（体重に基づく用量）を 12 週間又は 16 週間併用投与した時の有効性及び安全性を評価する第 III 相，無作為化，非盲検，多施設共同試験であり，国内 48 施設で実施した（図 1.5-4）。被験者は投与群 A（12 週間投与群）又は投与群 B（16 週間投与群）に 1：1 の比率で無作為に割り付けられた。

図 1.5-4. M14-153 試験のデザイン



OL Period：非盲検治療期，FU Period：後観察期，R：無作為化

本試験の主要な解析は，試験に組み入れられた全ての被験者が投与終了後 12 週を完了した後又は本試験を中止した後に実施した。また，2 回目の解析は本試験に組み入れられた全ての被験者が投与終了後 24 週を完了した後又は本試験を中止した後に実施した。本申請では，2 回目の解析（全ての被験者の投与期間中及び投与終了後 24 週まで）のデータを示した。

本試験の主要な目的は，肝硬変の認められない未治療の日本人 HCV ジェノタイプ 2 感染被験者において，OBV/PTV/r と RBV の 12 週間及び 16 週間併用投与後の SVR12 達成率について，pegIFN 及び RBV 投与時のヒストリカル SVR 達成率に基づいた臨床的に適切な閾値と比較すること並びに OBV/PTV/r と RBV の併用投与時の安全性を評価することであった。

その結果，有効性の主要評価項目において，16 週間投与群の SVR12 達成率は 91.5%（95%信頼区間：83.5%–99.5%）を示し，pegIFN と RBV 併用投与時のヒストリカル SVR 達成率に基づいた臨床的に適切な閾値（67%）を上回ったことから，16 週間投与群の優越性が検証された。一方，12 週間投与群の SVR12 達成率は 75.0%（95%信頼区間：62.8%–87.2%）であり，12 週間投与群の優越性は検証されなかった。肝硬変の認められない被験者では，いずれの投与群においても未治療例の SVR12 達成率（12 週間投与群：75.0%，16 週間投与群：91.5%）は既治療例の

SVR12 達成率（12 週間投与群：68.8%，16 週間投与群：75.8%）に比べて高かった。また，16 週間投与群では，肝硬変の認められない未治療例及び既治療例の部分集団のいずれにおいても HCV ジェノタイプ 2a 感染被験者で同様の高い SVR12 達成率を示し，HCV ジェノタイプ 2b 感染被験者における SVR12 達成率に比べて高かった（16 週投与群の未治療例：ジェノタイプ 2a；93.9%，ジェノタイプ 2b；85.7%，16 週投与群の既治療例：ジェノタイプ 2a；93.8%，ジェノタイプ 2b；53.6%）。OBV/PTV/r と RBV の併用投与時の忍容性は良好で，有害事象により投与を中止した被験者は認められなかった。

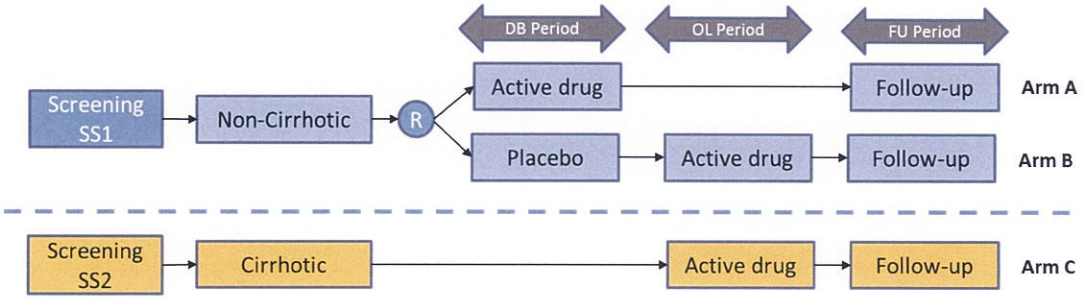
1.5.3.3.3.2 M13-004 試験

M13-004 試験の結果については，HCV ジェノタイプ 1 感染患者を対象とした OBV/PTV/r の初回申請時に提出した。

未治療及び既治療（代償性肝硬変を含む）の日本人 HCV ジェノタイプ 1b 感染患者を対象として，二重盲検期間中に RBV 非併用下で M14-153 試験と同じ用量の OBV/PTV/r 配合錠を 12 週間投与（投与群 A）したときの肝硬変の認められない被験者からの安全性データの一部は，M14-153 試験と M13-004 試験を比較することにより，OBV/PTV/r 投与時の安全性プロファイルに RBV の追加併用が及ぼす影響を評価することが可能となるため，本申請に含めることとした。

M13-004 試験は，未治療及び既治療（代償性肝硬変を含む）の日本人 HCV ジェノタイプ 1b 感染患者を対象として，OBV/PTV/r の有効性及び安全性を評価した第 III 相，多施設共同試験である。肝硬変の認められない被験者は，無作為化，二重盲検，プラセボ対照のサブ試験，また代償性肝硬変の認められる被験者は，非盲検のサブ試験に組入れられた。二重盲検期間では OBV/PTV/r 又はプラセボを 2：1 の割合で無作為に割付けし，プラセボに割付けられた被験者には，二重盲検期間終了後に非盲検下で OBV/PTV/r を投与した。肝硬変の認められない既治療例では，IFN 製剤の前治療に対する反応性（無効例，再燃例，IFN 不耐容例）を層別因子として無作為化し，また肝硬変の認められない未治療例では，高ウイルス量及び低ウイルス量を層別因子とし，高ウイルス量では更に IFN 製剤に対する適格性（適格例，不適格例）を層別因子として無作為化した。代償性肝硬変の認められる被験者は，非盲検下で OBV/PTV/r を投与した。本試験のデザインを図 1.5-5 に示した。

図 1.5-5. M13-004 試験のデザイン



R：無作為化，DB Period：二重盲検治療期，OL Period：非盲検治療期，FU Period：後観察期，SS：サブ試験

1.5.3.3.4 海外試験

HCV ジェノタイプ 1，2，3 又は 4 感染患者を対象として RBV 併用及び非併用下に DAA 2 剤の投与を行った海外の 3 試験（M13-393 試験，M11-652 試験，M12-998 試験）については，RBV 併用下に DAA 2 剤の本申請用量又はそれ以上の用量を投与した被験者の安全性データは，HCV ジェノタイプにかかわらず日本人被験者における DAA 2 剤と RBV 併用投与時の安全性を補足することから，本申請に含めた（表 1.5-1）。また，HCV ジェノタイプ 2 感染被験者に RBV 併用又は非併用下に OBV 25 mg，PTV 200 mg 及びリトナビル 100 mg を 1 日 1 回 12 週間投与した M12-998 試験データは，国内第 III 相試験の用法・用量の選択を補足することから，併せて本申請に含めた。

これらの 3 試験における DAA 2 剤及び/又は DAA 2 剤と RBV 併用投与時の安全性プロファイルは国内第 III 相試験の安全性プロファイルと全般的に一致していた。

M13-393 試験

M13-393 試験は，HCV ジェノタイプ 1b 又は 4 感染患者を対象として，RBV 併用又は非併用下に OBV と PTV/r 投与時の薬物動態，安全性及び有効性を評価した第 II 相，非盲検，併用投与試験であり，2 つのグループ（グループ 4 及び 6）で OBV，PTV/r 及び RBV を併用投与した。グループ 4 の被験者は未治療例で，グループ 6 の被験者は既治療例であった。いずれのグループも肝硬変の認められない被験者であり，OBV，PTV/r 及び RBV を 12 週間併用投与した。M13-393 試験における OBV，PTV/r 及び RBV 併用投与時の安全性プロファイルは，国内第 III 相試験で確認された安全性プロファイルと全般的に一致していた。

M12-998 試験

M12-998 試験は，未治療の HCV ジェノタイプ 1（1a 及び 1b），2 又は 3 感染患者を対象として，RBV 併用又は非併用下に OBV と PTV/r 投与時の抗ウイルス活性，安全性及び薬物動態を評

価した非盲検，多施設共同，2 群逐次，第 IIa 相試験であり，被験者に RBV 併用又は非併用下（それぞれ投与群 1 又は投与群 2）に OBV 25 mg と PTV/r 200/100 mg 1 日 1 回を 12 週間投与した。HCV ジェノタイプ 2 感染被験者において，RBV 非併用群に比べて RBV 併用群で高い SVR12 及び SVR24 達成率を示した（SVR12 及び SVR24 達成率は RBV 併用群においていずれも 80.0%［8/10 名］，RBV 非併用群においていずれも 60.0%［6/10 名］）。M12-998 試験における OBV と PTV/r 及び RBV 併用投与時の安全性プロファイルは，国内第 III 相試験で確認された安全性プロファイルと全般的に一致していた。

M11-652 試験

M11-652 試験は，肝硬変の認められない未治療又は pegIFN 及び RBV の前治療で無反応の HCV ジェノタイプ 1a 又は 1b 感染患者を対象として，RBV 併用又は非併用下に OBV と PTV/r 及び/又は dasabuvir（本邦では開発していない非ヌクレオシド系阻害剤）併用投与時の安全性及び有効性を評価した第 II 相，非盲検，無作為化試験である。2 つのグループ（グループ D 及び J）では，RBV 併用下に本申請用量以上の DAA 2 剤（OBV 25 mg 及び PTV/r 200/100 mg）を 12 週間投与した。グループ D は未治療例で，グループ J は pegIFN 及び RBV の前治療で無反応例であった。M11-652 試験における OBV と PTV/r 及び RBV 併用投与時の安全性プロファイルは，国内第 III 相試験の安全性プロファイルと全般的に一致していた。

1.5.3.4 対面助言

各臨床試験実施に先立ち医薬品医療機器総合機構（以下「機構」）と以下の対面助言を行った。

1.5.3.4.1 医薬品[redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

1. [redacted]
2. [redacted]
3. [redacted]

主な機構の見解：

- [redacted]
  - [redacted]

- [redacted]
- [redacted]

1.5.3.4.2 医薬品[redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

1. [redacted]
2. [redacted]

主な機構の見解：

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

1.5.3.4.3 [redacted]相談（20[redacted]年[redacted]月[redacted]日）

[redacted]について相談を行った。

1. [redacted]
2. [redacted]
3. [redacted]

主な機構の見解：

- [redacted]
- [redacted]

1.5.4 その他の海外での臨床開発状況

米国では，代償性肝硬変を含むジェノタイプ 1 型 C 型慢性肝炎（ジェノタイプ 1a 及び 1b）に対する IFN を使用しない DAA 3 剤併用療法として OBV/PTV/r 及び NS5B ポリメラーゼ阻害剤である dasabuvir の組み合わせ製剤の承認申請を 2014 年 4 月に行い，同年 12 月に承認を得た。また，ジェノタイプ 4 型 C 型慢性肝炎に対する治療として OBV/PTV/r の承認申請を 2015 年 2 月に行い，同年 7 月に承認を得た。

欧州では，ジェノタイプ 1 型 C 型慢性肝炎（ジェノタイプ 1a 及び 1b）に対する IFN を使用しない DAA 3 剤併用療法として OBV/PTV/r 及び dasabuvir の組み合わせ製剤及びジェノタイプ 4 型 C 型慢性肝炎に対する治療として OBV/PTV/r の承認申請を 2014 年 5 月に行い，2015 年 1 月に承認を得た。

1.5.5 本剤の予測される治療上の位置づけ

本邦で実施した第 III 相試験（M14-153 試験）の結果より，本剤と RBV の 16 週間併用投与は肝硬変の認められない未治療の HCV ジェノタイプ 2 感染被験者において高い SVR12 達成率（91.5%）を示し，未治療及び既治療の HCV ジェノタイプ 2a 感染被験者において同様の高い SVR12 達成率（93.9%及び 93.8%）を示した。また，本剤と RBV の併用による 16 週間経口投与時の忍容性は良好であった。この結果より，OBV/PTV/r 25/150/100 mg と RBV の併用療法は，HCV ジェノタイプ 2 感染患者に優れた効果を示すと考えられる。本剤は，[redacted]

([redacted]) の技術を用いて OBV，PTV 及びリトナビルを服薬が簡便な 1 つの錠剤に配合したことにより，HCV に対して異なる作用機序を有する OBV と PTV の 2 剤が確実に併用投与され，単剤の場合での併用服薬不遵守などによる曝露量の減少で引き起こされるウイルス耐性変異の出現リスクを抑制することが期待される。

これらの結果より，IFN を使用しない経口投与による本剤と RBV の併用使用は，肝硬変の認められない HCV ジェノタイプ 2 感染患者に対する新しい治療薬であることが裏付けられたため，本剤と RBV の併用レジメンは下記の効能・効果及び用法・用量について申請を行った。

【効能・効果】
セログループ 2（ジェノタイプ 2）の C 型慢性肝炎におけるウイルス血症の改善

【用法・用量】
リバビリンとの併用において，通常，成人には 1 日 1 回 2 錠（オムビタスビルとして 25mg，パリタプレビルとして 150mg 及びリトナビルとして 100mg）を食後に経口投与し，投与期間は 16 週間とする

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1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況

海外においては，オムビタスビル/パリタプレビル/リトナビル（以下「OBV/PTV/r」）とdasabuvir（HCV NS5B）錠の組合せ製剤もしくは本剤と EXVIERA（dasabuvir）錠の両剤の製造販売承認申請を行っている。承認取得済み（2016 年 7 月現在）の主要国を表 1.6-1 に示す。

表 1.6-1. 外国の承認状況

国・地域 申請年月/ 承認年月	販売名，承認製剤	効能効果
米国 2014 年 4 月/ 2014 年 12 月	VIEKIRA PAK（組合せ製剤） OBV/PTV/r フィルムコーティング配合錠(75mg/50mg/12.5mg) ＋ dasabuvir フィルムコーティング錠(250mg)	ジェノタイプ 1 型の代償性肝硬変を含む C 型慢性肝炎の治療
カナダ 2014 年 5 月/ 2014 年 12 月	HOLKIRA™ PAK（組合せ製剤） OBV/PTV/r フィルムコーティング配合錠(75mg/50mg/12.5mg) ＋ dasabuvir フィルムコーティング錠(250mg)	
米国 2015 年 2 月/ 2015 年 7 月	TECHNIVIE OBV/PTV/r フィルムコーティング配合錠 (75mg/50mg/12.5mg)	RBV 併用による，ジェノタイプ 4 型の肝硬変を含まない C 型慢性肝炎の治療
カナダ 2015 年 3 月/ 2015 年 10 月	TECHNIVIE OBV/PTV/r フィルムコーティング配合錠 (75mg/50mg/12.5mg)	RBV 併用による，肝硬変を含まない未治療又はペグインターフェロン製剤及びリバビリン既治療のジェノタイプ 4 型の C 型慢性肝炎の治療
EU 2014 年 5 月/ 2015 年 1 月 スイス 2014 年 5 月 2014 年 11 月	VIEKIRAX OBV/PTV/r フィルムコーティング配合錠 (75mg/50mg/12.5mg) EXVIERA dasabuvir フィルムコーティング錠 (250mg)	成人の C 型慢性肝炎の治療
米国 2015 年 9 月/ 2016 年 7 月	VIEKIRA XR OBV/PTV/r/dasabuvir フィルムコーティング配合錠 (50mg/33.33mg/8.33mg/200mg)	成人の C 型慢性肝炎の治療

1

1.6.2 海外における添付文書

1.6.2.1 米国における添付文書

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use （原文）

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIEKIRA PAK safely and effectively. See full prescribing information for VIEKIRA PAK.

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage, Removed-Limitations of Use (1)	10/2015
Dosage and Administration, Testing Prior to Initiation of VIEKIRA PAK (2.1)	10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2)	10/2015
Dosage and Administration, Hepatic Impairment (2.4)	10/2015
Contraindications (4)	10/2015
Warnings and Precautions (5.1)	10/2015

INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. VIEKIRA PAK includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor. (1)

DOSAGE AND ADMINISTRATION

Testing Prior to Initiation - Assess for laboratory and clinical evidence of hepatic decompensation. (2.1)
Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. (2.1)

Treatment Regimen and Duration by Patient Population

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[See Clinical Studies (14.3)]*.

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above. (2.1)
- Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:
- Ombitasvir, paritaprevir, ritonavir: 12.5/75/50 mg (3)
- Dasabuvir: 250 mg (3)

CONTRAINDICATIONS

- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. (4)
- Patients with moderate to severe hepatic impairment. (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate or strong inducers of CYP3A and strong inducers of CYP2C8; and strong inhibitors of CYP2C8. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Monitor for clinical signs and symptoms of hepatic decompensation. (5.1)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting VIEKIRA PAK (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on VIEKIRA PAK, monitor closely and follow recommendations in full prescribing information. (5.2)
- Risks Associated With Ribavirin Combination Treatment: If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- Drug Interactions: The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK. (5.4)

ADVERSE REACTIONS

In subjects receiving VIEKIRA PAK with ribavirin, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving VIEKIRA PAK without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of VIEKIRA PAK can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of VIEKIRA PAK. The potential for drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VIEKIRA PAK

Prior to initiation of VIEKIRA PAK, assess for laboratory and clinical evidence of hepatic decompensation *[see Warnings and Precautions (5.1 and 5.2)]*.

2.2 Recommended Dosage in Adults

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

The recommended oral dosage of VIEKIRA PAK is two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Take VIEKIRA PAK with a meal without regard to fat or calorie content *[see Clinical Pharmacology (12.3)]*.

VIEKIRA PAK is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with VIEKIRA PAK, the recommended dosage of RBV is based on weight: 1000 mg/day for subjects <75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 shows the recommended VIEKIRA PAK treatment regimen and duration based on patient population.

Table 1. Treatment Regimen and Duration by Patient Population (Treatment-Naïve or Interferon-Experienced)

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks

Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. **VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[see Clinical Studies (14.3)]*.		

2.3 Use in Liver Transplant Recipients

In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype *[see Clinical Studies (14.6)]*. When VIEKIRA PAK is administered with calcineurin inhibitors in liver transplant recipients, dosage adjustment of calcineurin inhibitors is needed *[see Drug Interactions (7)]*.

2.4 Hepatic Impairment

VIEKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

- Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side.
- Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

4 CONTRAINDICATIONS

- VIEKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity *[see Warnings and Precautions (5.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- VIEKIRA PAK is contraindicated with:
  - Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Drugs that are moderate or strong inducers of CYP3A and strong inducers of CYP2C8 and may lead to reduced efficacy of VIEKIRA PAK.
  - Drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.

Table 2 lists drugs that are contraindicated with VIEKIRA PAK *[see Drug Interactions (7)]*.

Table 2. Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions (5.2)]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase	Lovastatin,	Potential for myopathy including

Inhibitors	simvastatin	rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

- VIEKIRA PAK is contraindicated in patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported postmarketing in patients treated with VIEKIRA PAK. Most patients with these severe outcomes had evidence of advanced cirrhosis prior to initiating therapy with VIEKIRA PAK. Reported cases typically occurred within one to four weeks of initiating therapy and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

VIEKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) *[see Contraindications (4), Adverse Reactions (6.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage).
- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline and during the first 4 weeks of starting treatment and as clinically indicated.
- Discontinue VIEKIRA PAK in patients who develop evidence of hepatic decompensation.

5.2 Increased Risk of ALT Elevations

During clinical trials with VIEKIRA PAK with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects *[see Adverse Reactions (6.1)]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.

These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA PAK *[see Contraindications (4)]*. Alternative methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.

Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA PAK *[see Adverse Reactions (6.1)]*.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- Consider discontinuing VIEKIRA PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or INR.

5.3 Risks Associated With Ribavirin Combination Treatment

If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

5.4 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of VIEKIRA PAK and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during VIEKIRA PAK therapy; review concomitant medications during VIEKIRA PAK therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

5.5 Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients

The ritonavir component of VIEKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with VIEKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

6 ADVERSE REACTIONS

If VIEKIRA PAK is administered with ribavirin (RBV), refer to the prescribing information for ribavirin for a list of ribavirin-associated adverse reactions.

The following adverse reaction is described below and elsewhere in the labeling:

- Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis *[see Warnings and Precautions (5.1)]*
- Increased Risk of ALT Elevations *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of VIEKIRA PAK cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment was based on data from six Phase 3 clinical trials in more than 2,000 subjects who received VIEKIRA PAK with or without ribavirin for 12 or 24 weeks.

VIEKIRA PAK with Ribavirin in Placebo-Controlled Trials

The safety of VIEKIRA PAK in combination with ribavirin was assessed in 770 subjects with chronic HCV infection in two placebo-controlled trials (SAPPHIRE-I and -II) *[see Clinical Studies (14.1, 14.2)]*. Adverse reactions that occurred more often in subjects treated with VIEKIRA PAK in combination with ribavirin compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia (see Table 3). The majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE). The proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

Table 3. Adverse Reactions with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to Placebo for 12 Weeks

	SAPPHIRE-I and -II	
	VIEKIRA PAK + RBV 12 Weeks N = 770 %	**Placebo 12 Weeks N = 255 %**
Fatigue	34	26
Nausea	22	15
Pruritus*	18	7
Skin reactions[$]	16	9
Insomnia	14	8
Asthenia	14	7

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.
[$]Grouped terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria.

VIEKIRA PAK with and without Ribavirin in Regimen-Controlled Trials

VIEKIRA PAK with and without ribavirin was assessed in 401 and 509 subjects with chronic HCV infection, respectively, in three clinical trials (PEARL-II, PEARL-III and PEARL-IV) *[see Clinical Studies (14.1, 14.2)]*. Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with VIEKIRA PAK in combination with ribavirin (see Table 4). The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for both VIEKIRA PAK in combination with ribavirin and VIEKIRA PAK alone.

Table 4. Adverse Events with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to VIEKIRA PAK for 12 Weeks

	PEARL-II, -III and -IV	
	VIEKIRA PAK + RBV 12 Weeks N = 401 %	**VIEKIRA PAK 12 Weeks N = 509 %**
Nausea	16	8
Pruritus*	13	7
Insomnia	12	5
Asthenia	9	4

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

VIEKIRA PAK with Ribavirin in Subjects with Compensated Cirrhosis

VIEKIRA PAK with ribavirin was assessed in 380 subjects with compensated cirrhosis who were treated for 12 (n=208) or 24 (n=172) weeks duration (TURQUOISE-II) *[see Clinical Studies (14.1, 14.3)]*. The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with VIEKIRA PAK for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Skin Reactions

In PEARL-II, -III and -IV, 7% of subjects receiving VIEKIRA PAK alone and 10% of subjects receiving VIEKIRA PAK with ribavirin reported rash-related events. In SAPPHIRE-I and -II 16% of subjects receiving VIEKIRA PAK with ribavirin and 9% of subjects receiving placebo reported skin reactions. In TURQUOISE-II, 18% and 24% of subjects receiving VIEKIRA PAK with ribavirin for 12 or 24 weeks reported skin reactions. The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Laboratory Abnormalities

Serum ALT Elevations

Approximately 1% of subjects treated with VIEKIRA PAK experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. The incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol containing medication *[see Contraindications (4) and Warnings and Precautions (5.2)]*. The incidence of clinically relevant ALT elevations among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy was 3% (2/59).

ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. The majority of these ALT elevations were assessed as drug-related liver injury. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT *[see Warnings and Precautions (5.2)]*.

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15% of subjects receiving VIEKIRA PAK with ribavirin compared to 2% in those receiving VIEKIRA PAK alone. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with serum ALT elevations.

Anemia/Decreased Hemoglobin

Across all Phase 3 studies, the mean change from baseline in hemoglobin levels in subjects treated with VIEKIRA PAK in combination with ribavirin was -2.4 g/dL and the mean change in subjects treated with VIEKIRA PAK alone was -0.5 g/dL. Decreases in hemoglobin levels occurred early in treatment (Week 1-2) with further reductions through Week 3. Hemoglobin values remained low during the remainder of treatment and returned towards baseline levels by post-treatment Week 4. Less than 1% of subjects treated with VIEKIRA PAK with ribavirin had hemoglobin levels decrease to less than 8.0 g/dL during treatment. Seven percent of subjects treated with VIEKIRA PAK in combination with ribavirin underwent a ribavirin dose reduction due to a decrease in hemoglobin levels; three subjects received a blood transfusion and five required erythropoietin. One patient discontinued therapy due to anemia. No subjects treated with VIEKIRA PAK alone had a hemoglobin level less than 10 g/dL.

VIEKIRA PAK in HCV/HIV-1 Co-infected Subjects

VIEKIRA PAK with ribavirin was assessed in 63 subjects with HCV/HIV-1 co-infection who were on stable antiretroviral therapy. The most common adverse events occurring in at least 10% of subjects were fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%).

Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) subjects. Fifteen of these subjects were also receiving atazanavir at the time of bilirubin elevation and nine also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases *[see Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Studies (14.6)]*. No subject experienced a grade 3 ALT elevation.

Seven subjects (11%) had at least one post-baseline hemoglobin value of less than 10 g/dL, and six of these subjects had a ribavirin dose modification; no subject in this small cohort required a blood transfusion or erythropoietin.

Median declines in CD4+ T-cell counts of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively, and most returned to baseline levels post-treatment. Two subjects had CD4+ T-cell counts decrease to less than 200 cells/mm^3 during treatment without a decrease in CD4%. No subject experienced an AIDS-related opportunistic infection.

VIEKIRA PAK in Selected Liver Transplant Recipients

VIEKIRA PAK with ribavirin was assessed in 34 post-liver transplant subjects with recurrent HCV infection. Adverse events occurring in more than 20% of subjects included fatigue 50%, headache 44%, cough 32%, diarrhea 26%, insomnia 26%, asthenia 24%, nausea 24%, muscle spasms 21% and rash 21%. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten subjects underwent a ribavirin dose modification due to decrease in hemoglobin and 3% (1/34) had an interruption of ribavirin. Five subjects received erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion *[see Clinical Studies (14.5)]*.

6.2 Post-Marketing Adverse Reactions

The following adverse reactions have been identified during post approval use of VIEKIRA PAK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions (including angioedema).

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

See also Contraindications (4), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3).

7.1 Potential for VIEKIRA PAK to Affect Other Drugs

Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of VIEKIRA PAK with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

7.2 Potential for Other Drugs to Affect One or More Components of VIEKIRA PAK

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of VIEKIRA PAK with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes. Co-administration of VIEKIRA PAK with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of VIEKIRA PAK.

7.3 Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with VIEKIRA PAK, doses should be re-adjusted after administration of VIEKIRA PAK is completed. Dose adjustment is not required for VIEKIRA PAK.

Table 5 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of VIEKIRA PAK. See *Contraindications (4)* for drugs that are contraindicated with VIEKIRA PAK. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 5. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANTIPSYCHOTIC		
quetiapine*	↑ quetiapine	• Initiation of VIEKIRA PAK in patients taking quetiapine: Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for the recommendations on adverse reaction monitoring. • Initiation of quetiapine in patients taking VIEKIRA PAK: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
ANTIARRHYTHMICS		
amiodarone*, bepridil*, disopyramide*, flecainide*, lidocaine (systemic)*, mexiletine*, propafenone*, quinidine*	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with VIEKIRA PAK.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When VIEKIRA PAK is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
voriconazole*	↓ voriconazole	Co-administration of VIEKIRA PAK with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone*	↑ fluticasone	Concomitant use of VIEKIRA PAK with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative

		corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.
HIV-ANTIVIRAL AGENTS		
atazanavir/ritonavir once daily	↑ paritaprevir	When coadministered with VIEKIRA PAK, atazanavir 300 mg (without ritonavir) should only be given in the morning.
darunavir/ritonavir	↓ darunavir (C_{trough})	Co-administration of VIEKIRA PAK with darunavir/ritonavir is not recommended.
lopinavir/ritonavir	↑ paritaprevir	Co-administration of VIEKIRA PAK with lopinavir/ritonavir is not recommended.
rilpivirine	↑ rilpivirine	Co-administration of VIEKIRA PAK with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
rosuvastatin	↑ rosuvastatin	When VIEKIRA PAK is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day.
pravastatin	↑ pravastatin	When VIEKIRA PAK is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When initiating therapy with VIEKIRA PAK, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑ tacrolimus	When initiating therapy with VIEKIRA PAK, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on

		tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol*	↑ salmeterol	Concurrent administration of VIEKIRA PAK and salmeterol is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	No dose adjustment of buprenorphine/naloxone is required upon co-administration with VIEKIRA PAK. Patients should be closely monitored for sedation and cognitive effects.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
See Clinical Pharmacology, Tables 6 and 7. The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) (↑ *= increase of more than 20%,* ↓ *= decrease of more than 20%,* ↔ *= no change or change less than 20%).* *not studied.		

7.4 Drugs without Clinically Significant Interactions with VIEKIRA PAK

No dose adjustments are recommended when VIEKIRA PAK is co-administered with the following medications: digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, methadone, progestin only contraceptives, raltegravir, warfarin and zolpidem.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

There is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Adequate and well controlled studies with VIEKIRA PAK have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir, ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, VIEKIRA PAK should be used during pregnancy only if clearly needed.

If VIEKIRA PAK is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir, ritonavir, or dasabuvir. For ombitasvir, the highest dose tested produced exposures approximately 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses tested produced exposures approximately 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures approximately 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the recommended clinical dose.

8.3 Nursing Mothers

It is not known whether any of the components of VIEKIRA PAK or their metabolites are present in human milk. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIEKIRA PAK and any potential adverse effects on the breastfed child from VIEKIRA PAK or from the underlying maternal condition.

If VIEKIRA PAK is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

8.4 Pediatric Use

Safety and effectiveness of VIEKIRA PAK in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

No dosage adjustment of VIEKIRA PAK is warranted in geriatric patients. Of the total number of subjects in clinical studies of VIEKIRA PAK, 8.5% (174/2053) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is contraindicated in patients with moderate to severe (Child-Pugh B and C) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild, moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Other HCV Genotypes

The safety and efficacy of VIEKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

10 OVERDOSAGE

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

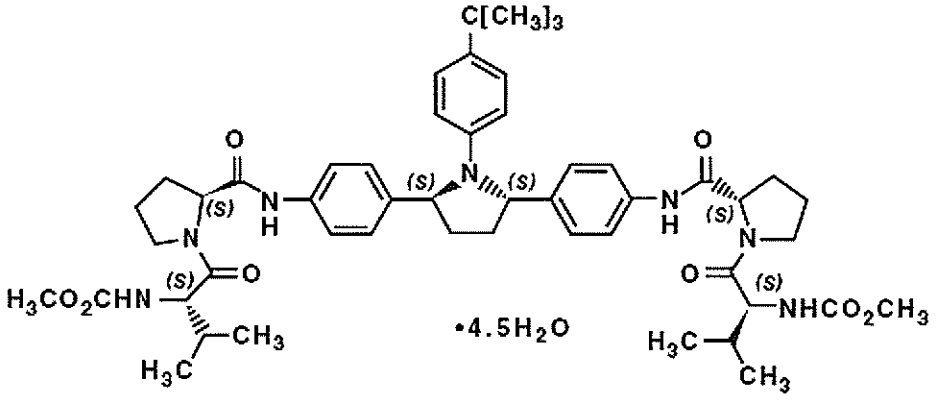
VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby

providing increased plasma concentration of paritaprevir. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage. Both tablets are for oral administration.

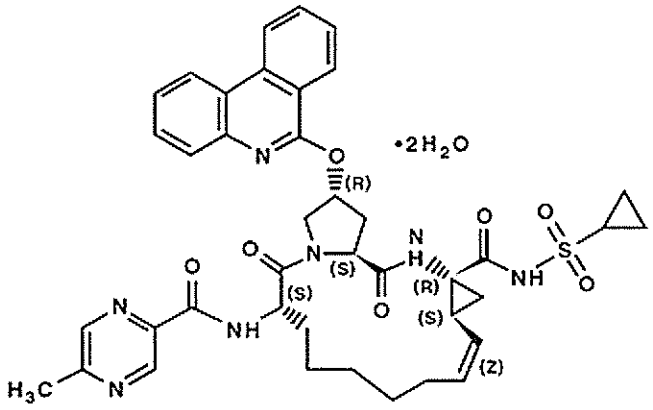
Ombitasvir

The chemical name of ombitasvir is Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate. The molecular formula is $C_{50}H_{67}N_7O_8 \cdot 4.5H_2O$ (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:



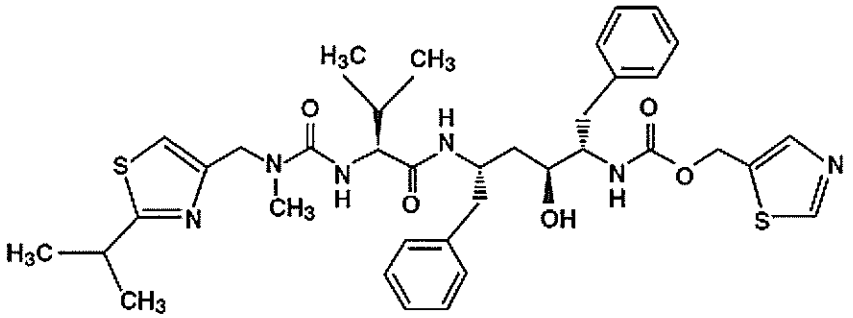
Paritaprevir

The chemical name of paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate. The molecular formula is $C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



Ritonavir

The chemical name of ritonavir is [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:



Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir, and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

Dasabuvir

The chemical name of dasabuvir is Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1). The molecular formula is $C_{26}H_{26}N_3O_5S{\bullet}Na{\bullet}H_2O$ (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate). The drug substance is white to pale yellow to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. Dasabuvir has the following molecular structure:

