この資料は、英国ヴィーブヘルスケアが 2013 年 10 月 22 日に発表したプレスリリースの日本語抄訳であり、報道関係者各位の利便性のために提供するものです。この資料の正式言語は英語であり、その内容およびその解釈については英語が優先します。詳細は http://www.viivhealthcare.com/をご参照下さい。

2013年10月25日

報道関係各位

ヴィーブヘルスケア株式会社

ヴィーブヘルスケア、HIV と共に生きる人々の為に、ドルテグラビルとアバカビル/ラミブジンの配合剤を米国で承認申請

＜2013 年 10 月 22 日英国ロンドン発＞

ヴィーブヘルスケアは本日、米国において、HIV-1 と共に生きる人々のためのドルテグラビル、アバカビル、ラミブジンを配合した開発中の単一錠剤レジメン（STR）の承認申請を提出したことを発表しました。この新薬承認申請（NDA）は、他の抗レトロウイルス薬との併用で年齢が 12 歳以上、体重が 40 キロ（約 88 ポンド）以上の成人および小児の HIV-1 治療を適応として、米国食品医薬品局（FDA）が 2013 年 8 月に Tivicay®の商標名で承認したドルテグラビルに続くものです。

「HIV と共に生きる人々とその主治医師は、個人に合わせた適切な治療選択肢を求める一方で、有効かつ忍容可能な抗ウイルス治療で必要な錠剤数を最低限に抑えようとしています」とヴィーブヘルスケアのチーフ・メディカル・オフィサー、John Pottage 博士は述べました。「この承認申請の目的は、初めて 1 日 1 回 1 錠の Tivicay ベースのレジメンを作り出すことです。」

欧州でもまもなく、この単一錠剤レジメンの 医薬品販売承認申請（MAA）が提出されます。2012 年 12 月に欧州で提出されたドルテグラビル（DTG）の MAA については、現在、欧州医薬品庁（EMA）で審査が進んでいます。アバカビル（ABC）とラミブジン（3TC）を含有する配合剤は、米国でエプジコム®(アバカビル硫酸塩 600 mg + ラミブジン 300 mg）、EU で Kivexa®の商標名で承認され、販売されています。

DTG/ABC/3TC を配合した開発中の単一錠剤は、時に「Trii」と称されてきました。本日発表された承認申請の提出は、このレジメンの安全性および有効性を評価した 1 件の主要な DTG の第 3 相試験 [1]とそれをサポートする他の 3 件の第Ⅲ/Ⅲb 試験 [2-4] に基づきます。さらには、DTG/ABC/3TC を単一錠剤レジメンとして服用した場合と、DTG と ABC/3TC を別の化合物として投与した場合とで生物学的同等性を比

較した主要なデータも含まれます[5]。また、治療歴のない HIV 感染女性を対象とした、この単一錠剤レジメンの 48 週間の第Ⅲb/Ⅳ試験（ARIA 試験）も現在継続中です[6]。

Tivicay®（ドルテグラビル）についての重要情報

効能・効果：TIVICAY は、他の抗レトロウイルス薬との併用で年齢が 12 歳以上、体重が 40 kg 以上の成人および小児の HIV-1 感染治療を適応とするヒト免疫不全ウイルス 1 型（HIV-1）インテグラーゼ阻害薬（INSTI）です。TIVICAY の開始に先立っては、Q148 置換と呼ばれる INSTI 耐性に加えて、L74I/M、E138A/D/K/T、G140A/S、Y143H/R、E157Q、G163E/K/Q/R/S、G193E/R を含む 2 つ以上の INSTI 耐性置換がある被験者で、TIVICAY 50 mg の 1 日 2 回治療に対するウイルス学的反応が不良であったことを考慮する必要があります。

エプジコム®（ABC+3TC）についての重要情報

効能・効果

- エプジコムは、他の抗レトロウイルス薬と併用で、HIV-1感染の治療を適応とします。エプジコムは、アバカビルを含有する複数の製剤のうちの一つです
- エプジコムの開始に先立っては、アバカビルによる過敏症の既往がある患者さんへの再投与を避けるため、以前のアバカビル含有製剤への暴露について、病歴を確認してください
- 1件の比較試験では、300 mgのアバカビル1日2回服用した場合よりも600 mgのアバカビルを1日1回服用した場合で、重度の過敏症の患者さんが多くみられました。
- 3剤レジメンの一部としてのEPZICOMについては、他のNRTIでなく、薬理学的クラスが異なるART薬との併用が推奨されます

ヴィーブヘルスケアについて

ヴィーブヘルスケアは、英国グラクソ・スミスクラインと米国ファイザーによって2009年に設立された、抗HIV薬に特化したスペシャリスト・カンパニーです。2012年10月に塩野義製薬株式会社が10%の持ち分を取得しました。ヴィーブヘルスケアは、どの会社よりも、HIV/AIDSについてより深い、幅広い関心を持つことで、新たなアプローチで効果的な新規のHIV治療薬を提供し、HIVの影響を受けているコミュニティを支援することを目指しています。詳細は、www.viivhealthcare.comをご覧ください。

TIVCAY の米国の添付文書は以下を参照ください。
https://www.viivhealthcare.com/media/58599/us_tivicay.pdf
エプジコムの米国の添付文書は以下を参照ください。
https://www.viivhealthcare.com/media/70430/us_epzicom.pdf

References

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6 ARIA (Study ING117172). A Study to Determine Safety and Efficacy of Dolutegravir/Abacavir/Lamivudine (DTG/ABC/3TC) in Human Immunodeficiency Virus (HIV)-1 Infected Antiretroviral Therapy (ART) Naïve Women. National Institutes of Health Study Identifier NCT01910402. More information available at: http://clinicaltrials.gov/show/NCT01910402

＜本件に関するお問い合わせ先＞

ヴィーブヘルスケア株式会社　担当：栗田
TEL: 03-5786-6043
http://glaxosmithkline.co.jp/viiv/

グラクソ・スミスクライン株式会社
広報部
担当：小松 / 福家
TEL：03-5786-5030/5041
http://glaxosmithkline.co.jp

*なお、米国におけるTIVCY®およびEPZICOM®の安全性情報について、プレスリリースの原文に以下のとおり記載がありますが、米国と状況が異なるため和訳は割愛させていただきました。

Important Safety Information:

Contraindication: Co-administration of TIVICAY with dofetilide (anti-arrhythmic) is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported and were characterised by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in 1% or fewer subjects receiving TIVICAY in Phase III clinical trials. Immediately discontinue TIVICAY and other suspect agents if signs or symptoms of hypersensitivity reaction develop, (including but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Monitor clinical status, including liver aminotransferases, and initiate appropriate therapy. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a hypersensitivity reaction to TIVICAY.

Effects on Serum Liver Biochemistries in Patients with Hepatitis B or C Coinfection: Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Fat Redistribution: Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy.

Immune Reconstitution Syndrome: During the initial phase of treatment, immune reconstitution syndrome can occur, which may necessitate further evaluation and treatment. Autoimmune

disorders have been reported to occur in the setting of immune reconstitution; the time to onset is more variable and can occur many months after initiation of treatment.

Adverse Reactions: The most commonly reported (≥2%) adverse reactions of moderate to severe intensity in treatment-naïve adult subjects in any one trial receiving TIVICAY in a combination regimen were insomnia (3%) and headache (2%).

Drug Interactions: Co-administration of TIVICAY with drugs that are strong inducers of UGT1A1 and/or CYP3A4 may result in reduced plasma concentrations of dolutegravir and require dose adjustments of TIVICAY.

TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

Pregnancy: Pregnancy category B. TIVICAY should be used during pregnancy only if the potential benefit justifies the potential risk. An Antiretroviral Pregnancy Registry has been established.

Breastfeeding: Breastfeeding is NOT recommended due to the potential for HIV transmission and the potential for adverse reactions in nursing infants.

Paediatric Patients: Safety and efficacy of TIVICAY has not been established in children younger than 12 years old, or weighing <40 kg, or in INSTI-experienced paediatric patients with documented or clinically suspected INSTI resistance.

IMPORTANT SAFETY INFORMATION FOR EPZICOM

Hypersensitivity Reactions

- EPZICOM contains abacavir sulfate, which has been associated with serious and sometimes fatal hypersensitivity reactions. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction
- Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir
- HLA-B*5701—negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701—positive patients
- Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible
- Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death
- Reintroduction of EPZICOM or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours
- Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n=206) in 9 clinical trials (range 2% to 9%) with enrollment from November 1999 to February 2002

Lactic Acidosis

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals

Coinfection with Hepatitis B or HCV

- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV and have discontinued lamivudine, which is one component of EPZICOM. Hepatic function should be monitored closely with both clinical and

laboratory follow-up for at least several months in patients who discontinue EPZICOM and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted

- Hepatic decompensation (some fatal) has occurred in HIV/HCV coinfected patients receiving combination antiretroviral therapy for HIV and interferon with or without ribavirin. Patients receiving interferon with or without ribavirin and EPZICOM should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of EPZICOM should be considered as medically appropriate

Impaired Hepatic Function

- EPZICOM Tablets are contraindicated in patients with hepatic impairment

Immune Reconstitution Syndrome

- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EPZICOM. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment
- Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment

Fat Redistribution

- Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy. The causal relationship, mechanism, and long-term consequences of these events are currently unknown

Cardiovascular

- An observational study showed an increase in MI with abacavir; a sponsor-conducted, pooled analysis did not show increased risk. In totality, the available data are inconclusive

- The underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking)

Impaired Renal Function

- Since EPZICOM is a fixed-dose tablet and the lamivudine component cannot be dose-adjusted, EPZICOM is not recommended for patients with creatinine-clearance <50 mL/min

Use With Other Abacavir-, Lamivudine- and/or Emtricitabine-Containing Products

- Do not use EPZICOM with other abacavir-, lamivudine- and/or emtricitabine-containing products

Adverse Events

- In one study of therapy-naïve patients (CNA30021), the most common adverse events (grade 2-4) reported with abacavir and lamivudine dosed once daily were hypersensitivity (9%), insomnia (7%), depression (7%), headache/migraine (7%), fatigue (6%), dizziness (6%), nausea (5%), diarrhea (5%), rash (5%), pyrexia (5%), abdominal pain (4%), abnormal dreams (4%), and anxiety (3%)