



## News Release

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## **Janssen Announces Submission of Supplemental New Drug Application to U.S. FDA by ViiV Healthcare for Expanded Use of CABENUVA (rilpivirine and cabotegravir) as an HIV Treatment for Use Every Two Months**

*If approved, expanded use would offer adults living with HIV an every-two-months long-acting injectable option for maintaining viral suppression*

**TITUSVILLE, N.J., February 24, 2021** – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that a supplemental New Drug Application (sNDA) has been submitted to the U.S. Food and Drug Administration (FDA) by ViiV Healthcare for the expanded use of CABENUVA (consisting of Janssen’s long-acting rilpivirine and ViiV Healthcare’s cabotegravir). The sNDA seeks to expand the CABENUVA label to include administration every two months for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in virologically suppressed adults (HIV-1 RNA less than 50 copies per mL) on a stable regimen, with no history of treatment failure, and with no known or suspected resistance to either cabotegravir or rilpivirine.

CABENUVA was approved by the FDA in January 2021 as a once-monthly, long-acting regimen for the treatment of HIV-1 infection in virologically suppressed adults.<sup>1</sup> The novel regimen was co-developed as part of a collaboration with ViiV Healthcare and builds on Janssen’s 25-year commitment to make HIV history. ViiV Healthcare is the marketing authorization holder for CABENUVA in the U.S.

“Today’s submission marks another important milestone on our journey to improving the lives of those living with HIV through the development of innovative new treatments,” said Brian Woodfall, M.D., Global Head, Development, Infectious Diseases, Janssen Biopharma, Inc. “First, with the introduction in the U.S. of CABENUVA as a once-monthly injection, and

now as we pursue approval for its use every two months, we're proud to be evolving the treatment options available for those affected by HIV."

The submission is based on the pivotal Phase 3b ATLAS-2M (Antiretroviral Therapy as Long-Acting Suppression) study, which demonstrated that CABENUVA taken every two-months had similar safety and efficacy rates in maintaining viral suppression in adults living with HIV-1 as compared to once-monthly CABENUVA treatment.<sup>2</sup> Non-inferiority was determined by comparing the proportion of participants with plasma HIV-1 RNA  $\geq 50$  copies per milliliter (c/mL) using the FDA Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population), which showed that the proportions were similar between the two arms: 1.7% (9/522) in the every-two-months arm and 1.0% (5/523) in the once-monthly arm (adjusted difference: 0.8%, 95% confidence interval [CI]: -0.6, 2.2).

As a key secondary endpoint, the study also showed that virologic suppression rates (HIV-1 RNA  $< 50$  c/mL) were similar between both groups and not dependent on which dose of CABENUVA was administered: 94.3% (492/522) and 93.5% (489/523) in the every two-months and monthly arms, respectively.

Treatment with CABENUVA was generally well-tolerated across both study arms. Rates of serious adverse events (SAEs) were 5.2% (27/522), and withdrawals due to adverse events (AEs) were 2.3% (12/522) in the every-two-months arm, similar to SAEs (3.6%; 19/523) and withdrawals due to AEs (2.5%; 13/523) experienced in the once-monthly arm.<sup>2</sup>

The every two-month version of rilpivirine and cabotegravir injectable treatment, in addition to the once-monthly treatment, was approved by the European Commission in December 2020 and was approved by the Australia Therapeutic Goods Administration earlier this month. Health Canada approved the once-monthly treatment in March 2020. Regulatory reviews continue in Switzerland, with several additional submissions planned throughout 2021.

#### **About ATLAS-2M (NCT03299049)**

The ATLAS-2M study is an ongoing Phase 3b, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the non-inferior antiviral activity and safety of long-acting cabotegravir and rilpivirine administered every eight weeks (two-months, 3 mL dose of each medicine) compared to every four weeks (once-monthly, 2 mL dose of each medicine) over a 48-week treatment period in 1,045 adults living with HIV-1.<sup>2</sup> Participants were required to be virologically suppressed for six months or greater, on first or second antiretroviral regimen, with no prior virologic failure. The primary outcome measure for the study is the proportion of participants with HIV-1 RNA  $\geq 50$  c/mL at Week 48 using the FDA Snapshot algorithm (ITT-E population).

For further information please see <https://clinicaltrials.gov/ct2/show/NCT03299049>.

#### **About CABENUVA (rilpivirine and cabotegravir)**

CABENUVA is approved as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. CABENUVA is administered by a healthcare provider as two intramuscular injections (cabotegravir, rilpivirine) in the buttocks.

The complete regimen combines rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) developed by Janssen Sciences Ireland UC, with the integrase strand transfer inhibitor (INSTI) cabotegravir, developed by ViiV Healthcare.

Rilpivirine is an NNRTI that works by interfering with an enzyme called reverse transcriptase, which in turn stops the virus from multiplying.

INSTIs inhibit HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This step is essential in the HIV replication cycle and is also responsible for establishing chronic infection.

### **Important Safety Information for CABENUVA**

CABENUVA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

### **CONTRAINDICATIONS**

- Do not use CABENUVA in patients with previous hypersensitivity reaction to cabotegravir or rilpivirine.
- Do not use CABENUVA in patients receiving carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, systemic dexamethasone (>1 dose), and St John's wort.

### **WARNINGS AND PRECAUTIONS**

#### **Hypersensitivity Reactions:**

- Hypersensitivity reactions, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported during postmarketing experience with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries.
- Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with CABENUVA.
- Discontinue CABENUVA immediately if signs or symptoms of hypersensitivity reactions develop. Clinical status, including liver transaminases, should be monitored and appropriate therapy initiated. Prescribe the oral lead-in prior to administration of CABENUVA to help identify patients who may be at risk of a hypersensitivity reaction.

#### **Post-Injection Reactions:**

- Serious post-injection reactions (reported in less than 1% of subjects) were reported within minutes after the injection of rilpivirine, including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events may have been associated with inadvertent (partial) intravenous administration and began to resolve within a few minutes after the injection.
- Carefully follow the Instructions for Use when preparing and administering CABENUVA to avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after the injection. If a post-injection reaction occurs, monitor and treat as clinically indicated.

**Hepatotoxicity:**

- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine with or without known pre-existing hepatic disease or identifiable risk factors.
- Patients with underlying liver disease or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations.
- Monitoring of liver chemistries is recommended and treatment with CABENUVA should be discontinued if hepatotoxicity is suspected.

**Depressive Disorders:**

- Depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation or attempt) have been reported with CABENUVA or the individual products.
- Promptly evaluate patients with depressive symptoms.

**Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:**

- The concomitant use of CABENUVA and other drugs may result in known or potentially significant drug interactions (see Contraindications and Drug Interactions).
- Rilpivirine doses 3 and 12 times higher than the recommended oral dosage can prolong the QTc interval. CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes.

**Long-Acting Properties and Potential Associated Risks with CABENUVA:**

- Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer). Select appropriate patients who agree to the required monthly injection dosing schedule because non-adherence to monthly injections or missed doses could lead to loss of virologic response and development of resistance.
- To minimize the potential risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injection doses of CABENUVA. If virologic failure is suspected, switch the patient to an alternative regimen as soon as possible.

**ADVERSE REACTIONS**

The most common adverse reactions (incidence  $\geq 2\%$ , all grades) with CABENUVA were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash.

**DRUG INTERACTIONS**

- Refer to the applicable full Prescribing Information for important drug interactions with CABENUVA, Vocabria, or rilpivirine.
- Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.
- Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease the plasma concentrations of cabotegravir. Drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine.
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** There are insufficient human data on the use of CABENUVA during pregnancy to adequately assess a drug-associated risk for birth defects and

miscarriage. Discuss the benefit-risk of using CABENUVA during pregnancy and conception and consider that cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA. An Antiretroviral Pregnancy Registry has been established.

- **Lactation:** The CDC recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Breastfeeding is also not recommended due to the potential for developing viral resistance in HIV-positive infants, adverse reactions in a breastfed infant, and detectable cabotegravir and rilpivirine concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA.

Please see full [Prescribing Information](#).

### **About the Janssen Pharmaceutical Companies of Johnson & Johnson**

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at [www.janssen.com](http://www.janssen.com) and follow us at [www.twitter.com/JanssenGlobal](https://www.twitter.com/JanssenGlobal) and [www.twitter.com/JanssenUS](https://www.twitter.com/JanssenUS). Janssen Biopharma, Inc. and Janssen Sciences Ireland UC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

To learn more about Janssen's commitment to the prevention and treatment of HIV, please visit [jnj.com/HIV](http://jnj.com/HIV).

### **Cautions Concerning Forward-Looking Statements**

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding rilpivirine and development of potential preventive and treatment regimens for HIV. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Sciences Ireland UC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 3, 2021, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at [www.sec.gov](http://www.sec.gov), [www.jnj.com](http://www.jnj.com) or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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## REFERENCES

1. CABENUVA (cabotegravir, rilpivirine) Prescribing Information. US Approval January 2021.
2. Overton E et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *The Lancet*. 2020;396(10267):1994-2005.

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