INTERDISCIPLINARY MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION,
CENTER FOR DRUG EVALUATION AND RESEARCH,
OFFICE OF INFECTIOUS DISEASES,
DIVISION OF ANTIVIRALS

Application Number(s)	NDA 202022 S-017 (SDN 492) NDA 202022 S-018 (SDN 493)
Priority or Standard	Priority
Submit Date(s)	10/15/2021
Received Date(s)	10/15/2021
PDUFA Goal Date	03/29/2022
Division/Office	DAV/OID
Established Name	Rilpivirine
Trade Name	EDURANT
Pharmacologic Class	Non-nucleoside reverse transcriptase inhibitor (NNRTI)
Applicant	Janssen
Formulation(s)	Oral tablet
NEW Dosing Regimen	Expand the population to adolescents 12 years of age and older and weighing at least 35 kg
Regulatory Action	Approval
Approved Indication(s)/population(s) with current Application	EDURANT is indicated in combination with VOCABRIA (cabotegravir) for short-term treatment of HIV-1 infection in adults **and adolescents 12 years and older and weighing at least 35 kg** who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: • oral lead-in to assess the tolerability of rilpivirine prior to administration of rilpivirine extended-release injectable suspension, a component of CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) • oral therapy for patients who will miss planned injection dosing with CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)
Links	\\CDSESUB1\evsprod\NDA202022\0207 every-4-week dosing (Q4W) \\CDSESUB1\evsprod\NDA202022\0208 every-8-week dosing (Q8W)

Background
EDURANT (rilpivirine, RPV), originally approved on May 20, 2011, is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in ARV treatment-naïve patients 12 years of age and older and weighing at least 35 kg with plasma HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

On January 21, 2021, the Applicant (Janssen) received approval for efficacy supplement (S-014) for EDURANT (rilpivirine, RPV) 25 mg tablet to be used in combination with VOCABRIA (cabotegravir; CAB) 30 mg tablet for the short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV, for use as an:

- oral lead-in to assess the tolerability of RPV prior to administration of RPV extended-release injectable suspension, a component of CABENUVA (CAB extended-release injectable suspension; RPV extended-release injectable suspension).
- oral therapy for patients who will miss planned injection dosing with CABENUVA (CAB extended-release injectable suspension; RPV extended-release injectable suspension).

On October 15, 2021, the Applicant submitted efficacy supplements (S-017 and S-018) for EDURANT to update the USPI and expand the population to adolescents 12 years of age and older and weighing at least 35 kg when used in combination with cabotegravir (VOCABRIA and CABENUVA). CABENUVA is a co-packaged product containing extended-release injectable suspensions of CAB and RPV; ViiV Healthcare is collaborating with Janssen to develop CABENUVA.

Prior to these submissions, EDURANT was already approved for the treatment of HIV-1 infection in adolescents 12 years of age and older and weighing at least 35 kg. In addition, CABENUVA every-4-week (Q4W) injection dosing was approved for the treatment of HIV-1 infection in adults. During the review cycle, VOCABRIA and CABENUVA every-8-week (Q8W) injection dosing was approved for HIV-1 treatment in adults under NDA 212887 S-001 and NDA 212888 S-001, respectively; in addition, APRETUDE (CAB extended-release injectable suspension; Q8W) was approved for HIV-1 prevention for adults and adolescents weighing at least 35 kg under NDA 215499.

Supplemental NDAs (sNDAs) for EDURANT
The Applicant relied on cross-referencing and submitted these sNDAs for EDURANT in parallel with ViiV Healthcare's sNDA submissions for CABENUVA (S-005 and S-006) and VOCABRIA (S-005 and S-006). Thus, no clinical trial data are contained in the sNDAs for EDURANT.

The Week 16 interim data (CSR) from cohort 1 of Study 208580 (MOCHA, NCT03497676) are submitted under NDAs 212887 (VOCABRIA) and 212888 (CABENUVA). For the assessment of the clinical and pharmacokinetic data, refer to the reviews filed under NDAs 212887 and 212888 (Clinical Pharmacology Review March 8, 2022; Clinical Review March 24, 2022).

In sum, the results from MOCHA support expanding the population to adolescents 12 years of age and older and weighing at least 35 kg for CABENUVA as proposed in the respective USPIs for CABENUVA, VOCABRIA and EDURANT, summarized below (bold font used for emphasis):

> *EDURANT is indicated in combination with VOCABRIA (cabotegravir) for short-term treatment of HIV-1 infection in adults **and adolescents 12 years and older and weighing at least 35 kg** who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:*
>
> - *oral lead-in to assess the tolerability of rilpivirine prior to administration of rilpivirine extended-release injectable suspension, a component of CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)*
> - *oral therapy for patients who will miss planned injection dosing with CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)*

Prescribing Information Labeling Review
The Applicant's proposed label submitted on October 15, 2021 was compared with the final agreed upon labeling for EDURANT. The general changes to the EDURANT labeling were made to align with the CABENUVA labeling and are highlighted below in bold font:

1 INDICATIONS AND USAGE

1.2 *Treatment of HIV-1 in Combination with Cabotegravir*

EDURANT is indicated in combination with VOCABRIA (cabotegravir) for short-term treatment of HIV-1 infection in adults **and adolescents 12 years and older and weighing at least 35 kg** who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as *[see Dosage and Administration (2.2)]*:

2 DOSAGE AND ADMINISTRATION

2.2 *Recommended Dosage in Combination with Cabotegravir in Adults **and Adolescents 12 Years of Age and Older and Weighing at Least 35 kg***

Oral Dosing to Replace Planned Missed Injections of CABENUVA
Planned Missed Injections for Patients on Monthly Dosing Schedule
If a patient plans to miss a scheduled monthly injection of CABENUVA by more than 7 days, take daily oral therapy for up to 2 months to replace missed injection visits. The recommended oral daily dose is one 25 mg tablet of EDURANT and one 30 mg tablet of VOCABRIA (cabotegravir). Take EDURANT with VOCABRIA (cabotegravir) at

approximately the same time each day with a meal. The first dose of oral therapy should be initiated at approximately the same time as the planned missed injection and continued until the day injection dosing is restarted. For oral therapy with EDURANT and VOCABRIA of durations greater than 2 months, an alternative oral regimen is recommended**, which may include EDURANT**. See full prescribing information for CABENUVA to resume monthly injection dosing.

6 ADVERSE REACTIONS

6.1 *Clinical Trials Experience*

Clinical Trials Experience in Pediatric Patients
The safety assessment is based on the Week 48 analysis of the single-arm, open-label, Phase 2 trial, TMC278 C213, in which 36 antiretroviral treatment naïve HIV 1 infected patients 12 to less than 18 years of age and weighing at least 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral agents *[see Clinical Studies (14.3)]*. The median duration of exposure was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

ADRs were reported in nineteen pediatric subjects (52.8%). Most ADRs were Grade 1 or 2. The most common ADRs reported in at least 2 subjects (regardless of severity) include headache (19.4%), depression (19.4%), somnolence (13.9%), nausea (11.1%), dizziness (8.3%), abdominal pain (8.3), vomiting (5.6%) and rash (5.6%).

Observed laboratory abnormalities were comparable to those in adults.

Trial 208580 [MOCHA]
Based on data from the Week 16 analysis of the MOCHA study in 15 adolescents (aged 12 to younger than 18 years and weighing ≥35 kg) receiving EDURANT (25 mg once daily) in addition to continuing background antiretroviral therapy, the safety profile during the oral-lead in period in adolescents was consistent with the safety profile established with EDURANT in adults.

8 USE IN SPECIFIC POPULATIONS

8.4 *Pediatric Use*

The safety, efficacy and pharmacokinetics of EDURANT were evaluated in a single arm, open label, Phase 2 trial that enrolled 36 antiretroviral treatment-naïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg *[see Dosage and Administration (2.1), Adverse Reactions (6.12), Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*.

MOCHA Trial (NCT03497676) in Adolescents

The safety, tolerability, and pharmacokinetics of oral and injectable cabotegravir and oral and injectable rilpivirine are being assessed in an ongoing Phase 1/2 multicenter, open-label, non comparative study, MOCHA (IMPAACT 2017) *[see Adverse Reactions (6.1)]*. Refer to the VOCABRIA and CABENUVA prescribing information for additional information when EDURANT is used in combination with cabotegravir.

Safety and effectiveness in pediatric patients less than 12 years of age or weighing less than 35 kg have not been established.

Planned Regulatory Action
For the submission of these sNDAs for EDURANT, the interdisciplinary team did not identify any issues that precluded approval.

The approval of these sNDAs for EDURANT is contingent on the approvals of the sNDAs for CABENUVA and VOCABRIA because the expanded indication for CABENUVA for EDURANT is linked to its use in combination with VOCABRIA.

Please refer to the Approval action letter for respective CABENUVA and VOCABRIA sNDAs for additional details.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIMOTHY J JANCEL
03/29/2022 09:16:47 AM

SARAH M CONNELLY
03/29/2022 09:18:24 AM

YODIT BELEW
03/29/2022 10:06:58 AM