# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206352Orig1s000
# 021567Orig1s035

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Risk Evaluation and Mitigation Strategy (REMS) Review

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| Date: | June 2, 2014 |
| Reviewer(s): | Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK) |
| Team Leader: | Reema Mehta, Pharm.D., M.P.H., DRISK |
| Division Director: | Claudia Manzo, Pharm.D., DRISK |
| Drug Name(s): | Reyataz (atazanavir) |
| Subject: | Review evaluates if a REMS is needed for Reyataz |
| Therapeutic Class: | protease inhibitor |
| Dosage and Route: | powder for oral use |
| Application Type/Number: | NDA 206-352 and NDA 21-567/S-035 |
| Applicant/sponsor: | Bristol-Myers Squibb |
| OSE RCM #: | 2013-2744 |

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# 1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Reyataz (atazanavir) powder for oral use, NDA 206-352 and NDA 21-567/S-035 . A 505(b)(1) application for Reyataz was received by the Division of Antiviral Products (DAVP) from Bristol-Myers Squibb on December 2, 2013 to treat Human Immunodeficiency Virus (HIV)-1 infection. The Sponsor did not propose a REMS for Reyataz.

## 1.1 PRODUCT BACKGROUND

Reyataz®(atazanavir) is an azapeptide inhibitor of HIV-1 protease (US approval June 2003) currently marketed as 150 mg, 200 mg, and 300 mg oral capsules in combination with other antiretroviral agents, for the treatment of HIV infection in adults and pediatric patients 6 to less than 18 years of age. Reyataz® should not be administered to pediatric patients less than 3 months of age due to the risk of kernicterus (neurological condition caused excessive bilirubin levels).

Reyataz powder for oral use (POU) has been developed for use in combination with other antiretroviral (ARV) agents, to treat HIV-1 infection in pediatric patients 3 months and older weighing at least 10 kg. Recommended dosage and administration of Reyataz POU is as follows:

- Daily dose is based on body weight (see Table 1).
- Powder must be mixed with the smallest amount of food or beverage possible (such as applesauce, yogurt, milk, liquid infant formula, or water), and taken with ritonavir (RTV)[1].
- The mixture should be administered within 1 hour of mixing.

**Table 1: Reyataz POU Dosage for Pediatric Patients (10 kg to less than 25 kg)**

| Body Weight | Reyataz[a] dose | Ritonavir[b] dose |
|---|---|---|
| 10 kg to less than 15 kg | 200 mg (4 packets) | 80 mg |
| 15 kg to less than 25 kg | 250 mg (5 packets) | 80 mg |

[a] Each packet contains 50 mg of Reyataz in 1.5 g of powder.
[b] Ritonavir solution

Reyataz POU is not recommended for use in adults or in children weighing less than 10 kg or who weigh 25 kg or more. Ritonavir doses greater than 100 mg once daily are not recommended as higher doses may alter the safety profile of Reyataz.

[1] Ritonavir is a protease inhibitor used to treat HIV infection. It is often prescribed in combination with other antiretroviral agents as a "booster" due to its ability to inhibit the metabolism of other protease inhibitors; this inhibition leads to higher plasma concentrations of the target protease inhibitor, allowing for a lower dose and frequency, resulting in improved clinical efficacy.

## 1.2 DISEASE BACKGROUND

Human Immunodeficiency Virus (HIV) is a ribonucleic acid (RNA)-containing virus that uses the enzyme reverse transcriptase to copy its RNA into the host cell DNA. HIV primarily infects cells of the immune system and within approximately 48 hours of infection, replicating virus can be found throughout the lymphoid tissue. Without treatment, HIV infection causes generalized immune dysfunction eventually leading to the development of conditions meeting the clinical criteria[2] for a diagnosis of Acquired Immune Deficiency Syndrome (AIDS).

The Centers for Disease Control and Prevention (CDC) estimates that more than 1.1 million people in the United States are living with HIV infection.[3] The majority of HIV-infected children acquire the disease through mother-to-child transmission either before birth, during birth or from breastfeeding. Children however, represent a relatively small percentage of the total number of HIV/AIDS cases in the U.S. due to the widespread use of zidovudine (AZT, azidothymidine) and other highly active antiretroviral therapies to treat HIV-infected pregnant women. In 2010, there were an estimated 2,895 children under 13 years of age living with HIV infection in the U.S.[4]

Clinical manifestations of HIV-1 in pediatric patients can vary widely based on factors such as age[5], however common symptoms may include 1) failure to grow/gain weight based on standardized growth charts, 2) failure to meet developmental milestones, 3) frequent diarrhea, ear infections and other common childhood illnesses, and 4) nervous system problems including seizures. As the disease progresses these patients may develop opportunistic infections such as serious infection due to cytomegalovirus (type of herpes virus) or pneumocystis pneumonia (fungal infection of the lungs); conditions that rarely affect healthy children with intact immune systems.

HIV treatment is aimed at preventing a progressive deterioration of the immune system and providing prophylactic measures to prevent opportunistic infections in the later stages of HIV infection. A three-drug combination regimen (including at least two drugs with different mechanisms of action) is considered standard therapy for achieving complete viral suppression.

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[2] The Centers for Disease Control and Prevention (CDC) surveillance case definition for AIDS incorporates an HIV infection staging classification system. HIV infection, stage 3 (AIDS) meets the following laboratory criteria: CD4+ T-lymphocyte count of <200 cells/µL or CD4+ T-lymphocyte percentage of total lymphocytes of <14, or documentation of an AIDS-defining condition. Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of ≥200 cells/µL and a CD4+ T-lymphocyte percentage of total lymphocytes of ≥14.

[3] Centers for Disease Control and Prevention, HIV in the Unites States: *At A Glance* (last updated December 3, 2013). Available at: http://www.cdc.gov/HIV/resources/factsheets/PDF/HIV_at_a_glance.pdf.

[4] Centers for Disease Control and Prevention, HIV Surveillance Report: Diagnosis of HIV Infection in the United States and Dependent Areas, 2011 (Vol. 23). Available at: http://www.cdc.gov/hiv/pdf/statistics_2011_HIV_Surveillance_Report_vol_23.pdf#Page=52.

[5] Newborns with perinatal HIV infection rarely present with symptoms at birth.

The Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infection Children provides the following general guidelines (see Table 2) for initiating ARV therapy in HIV-infected children.[6]

**Table 2: Guidelines for Initiation of Antiretroviral Therapy in HIV-Infected Children**

| Age | Criteria | Recommendation |
|---|---|---|
| **<12 months** | Regardless of clinical symptoms, immune status, or viral load | Treat |
| **1 to <3 years** | AIDS or significant HIV-related symptoms | Treat |
| | CD4 cell count<1000 cells/mm **or** CD4 percentage<25% | Treat |
| | Asymptomatic or mild symptoms **and** CD4 cell count≥1000 cells/mm or CD4 percentage≥25% | *Consider treatment* |
| **3 to <5 years** | AIDS or significant HIV-related symptoms | Treat |
| | CD4 cell count<750 cells/mm **or** CD4 percentage<25% | Treat |
| | Asymptomatic or mild symptoms **and** CD4 cell count≥750 cells/mm or CD4 percentage≥25% | *Consider treatment* |
| **≥5 years** | AIDS or significant HIV-related symptoms | Treat |
| | CD4 cell count<500 cells/mm | Treat |
| | Asymptomatic or mild symptoms **and** CD4 cell count>500 cells/mm or CD4 percentage≥25% | *Consider treatment* |
| **All Ages** | HIV RNA levels>100,000 copies/mL | Treat |

A challenge to successful long-term treatment is the emergence of drug resistance given high spontaneous mutation rates with HIV. Pediatric patients on ARV therapy should have laboratory monitoring every 3-4 months to confirm maintenance of CD4 T cell counts[7] and viral suppression. If virus is consistently detected, the root cause must be determined and a change in medication therapy may be warranted.[8]

[6] Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed April 28, 2014 [Table 5, p.56].

[7] CD4 T cells are specialized "helper" cells of the immune system that initiate the body's response to infections; CD4 cells also serve as "host" cells that aid in HIV replication.

[8] McFarland EJ. Chapter 41. Human Immunodeficiency Virus Infection. In: Hay WW, Jr, Levin MJ, Deterding RR, Abzug MJ, Sondheimer JM. eds. *CURRENT Diagnosis & Treatment: Pediatrics, 21e.* New York, NY: McGraw-Hill; 2012. http://accessmedicine mhmedical.com/content.aspx?bookid=497&Sectionid=40851708. Accessed April 28, 2014.

The following drug products (see Table 3) are approved to treat pediatric HIV infection[9]; one product (tenofovir disoproxil fumarate and emtricitabine)[10] is marketed under a REMS program:

**Table 3: Approved Antiretroviral Drugs for Pediatric Treatment of HIV Infection**

| | | |
|---|---|---|
| **Protease Inhibitors (PIs)** | | |
| • atazanavir (ATV)<br>• amprenavir (APV)<br>• tipranavir (TPV)<br>• indinavir (IDV) | • lopinavir and ritonavir (LPV/r)<br>• fosamprenavir (FPV)<br>• ritonavir (RTV) | • darunavir (DRV)<br>• nelfinavir (NFV)<br>• saquinavir (SQV) |
| **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** | | |
| • lamivudine and zidovudine<br>• emtricitabine (FTC)<br>• lamivudine (3TC)<br>• abacavir and lamivudine | • zidovudine (ZDV), azidothymidine (AZT)<br>• abacavir, zidovudine, and lamivudine<br>• tenfovir disoproxil fumarate and emtricitabine | • didanosine (ddI)<br>• tenfovir disoproxil fumarate (TDF)<br>• stavudine (d4T)<br>• abacavir (ABC) |
| **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | | |
| • rilpivirine (RPV)<br>• etravirine (ETV) | • delavirdine (DLV)<br>• efavirenz (EFV) | • nevirapine (NVP) |
| **Fusion Inhibitors** | **Entry Inhibitors** | **HIV Integrase Strand Transfer Inhibitors (INSTIs)** |
| • enfuvirtide , T-20 (ENF) | • maraviroc (MVC) | • raltegravir (RAL)<br>• dolutegravir (DTG) |
| **Fixed Dose Combinations Providing Complete Regimen** | | |
| • efavirenz, emtricitabine, tenofovir disoproxil fumarate | • emtricitabine, rilpivirine, tenofovir disoproxil fumarate | • elvitegravir, cobicistate, emtricitabine, tenofovir disoproxil fumarate |

## 1.3 REGULATORY HISTORY

June 20, 2003: NDA 21-567 approved for Reyataz®(atazanavir sulfate) 100 mg, 150 mg and 200 mg capsules in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults.

[9] Food and Drug Administration (FDA), For Consumers: Approved antiretroviral drugs for pediatric treatment of HIV infection. Available at: http://www fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118951 htm

[10] Truvada® (emtricitabine /tenofovir disoproxil fumarate) is approved with a REMS for a Pre-Exposure Prophylaxis (PrEP) indication.

March 25, 2008: NDA 21-567/S-015 approved for Reyataz to treat HIV-1 infection in pediatric patients (ages 6 to 18 years of age).

- The clinical development program included one dose-ranging, pharmacokinetic, safety, and viral activity trial (study AI424020) [also designated as Pediatric AIDS Clinical Trials Group (PACTG) 1020-A] in treatment-experienced and treatment-naïve patients 3 months to less than 18 years of age.
- The PACTG study evaluated the approved Reyataz capsule formulation and an investigational powder formulation. Data from the powder formulation cohort was incomplete and was to be formally submitted at a later time.
- The dosing of treatment-experienced patients weighing (b) (4) could not be supported based on data submitted under S-015.
- DAVP concluded that no serious post-marketing concerns emerged; therefore, no new risk management activities were required beyond the patient package insert with the approved Reyataz capsules. Information on cases of toxic skin eruptions related to Reyataz use was added to the product labeling under S-01 based on data from post-marketing AERS reports.

December 2, 2013: Bristol-Myers Squibb submitted 505(b)(1) NDA 206-352 for Reyataz powder for oral use to treat pediatric patients weighing 10 kg to less than 25 kg, and NDA 21-567/S-035 for 1) labeling consistency, 2) to fulfill a post-marketing commitment under S-015[11], and 3) partially fulfill a Written Request for Exclusivity.

## 2 MATERIALS REVIEWED

The following are a list of materials used to inform the review:

- Shapiro A. Clinical Review for Reyataz (atazanavir) NDA 206-352, dated May 9, 2014.
- Draft Labeling for Reyataz (atazanavir) POU, dated May 9, 2014
- Shapiro A. Safety Overview for Reyataz (atazanavir) NDA 206-352, dated March 31, 2014
- Shapiro A. Mid-cycle review for Reyataz (atazanavir) NDA 206-352, dated March 4, 2014
- Bristol-Myers Squibb. Clinical Overview for Reyataz (atazanavir), NDA 206-352, dated October 22, 2013
- Bristol-Myers Squibb. Safety Overview for Reyataz (atazanavir), NDA 206-352, dated October 22, 2013
- Bristol-Myers Squibb. Approved Labeling for Reyataz (atazanavir) capsules, dated August 2013

[11] Deferred pediatric study or studies under the Pediatric Research Equity Act (PREA) for the treatment of HIV-1 infection in pediatric patients ages greater than or equal to 3 months to 18 years to obtain a minimum of 100 patients followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development.

- Shapiro A. Amended Clinical Review for Reyataz (atazanavir) NDA 21-567, dated April 29, 2008
- Approval Letter for NDA 21-567/S-015, dated March 25, 2008
- Approval Letter for NDA 21-567, dated June 20, 2003

## 3 OVERVIEW OF CLINICAL PROGRAM

Clinical development for the approved Reyataz capsule formulation in pediatric patients (aged 6 years and older) was based on the following clinical study:

- Study AI424020 (referred to as the *Pediatric AIDS Clinical Trials Group 1020-A or "PACTG"*); Phase1/2, open-label, pharmacokinetic and safety study to determine the optimal dose of Reyataz capsules and "investigational powder formulation" (administered with and without RTV) in combination regimens, for use in ARV-naïve or -experienced pediatric patients with HIV infection.

Safety and Efficacy of Reyataz POU was established based on the following Phase 3 studies:

| | **Study AI424397 (PRINCE I)** | **Study AI424451 (PRINCE II)** |
|---|---|---|
| **Study Design**[12] | Phase 3b, prospective, international, multi-center, non-randomized, efficacy, safety and pharmacokinetic study of Reyataz POU and RTV optimized therapy in ARV-naïve or –experienced pediatric HIV patients; week 48 analysis. | Same as PRINCE I; interim analysis with a June 17, 2013 data cutoff date |
| **Study Population**[13] | Pediatric HIV patients (≥3 months to <5 years and 6 months of age), weighing (≥5 to <25kg); approximately 2/3 treatment-naïve. | Pediatric HIV patients (≥3 months to <11 years), weighing (≥5 to <35kg); approximately 3/5 treatment-naïve. |
| **Treatment protocol** | Reyataz POU (50 mg/packet) at doses recommended per protocol: Once daily Reyataz dose of 150 mg for 5 to <10 kg; 200 mg for 10 to <15 kg; 250 mg for 15 to <25 kg weight + once daily dose of RTV oral solution (80 mg/mL) | Same as PRINCE I |
| **Endpoints** | 48 week virologic success rate (two success criteria were used; "success" defined as HIV RNA<50 copies/mL and <400 copies/mL at week 48) | Same endpoint as PRINCE I (*interim results at week 48*) |
| **Sample Size** | Total treated: 56 | Total treated: 78 |

### 3.1 EFFICACY

In the PRINCE I study, virologic success (HIV RNA<50 copies/mL) at 48 weeks was achieved by 68% and 71% of patients weighing 10 to <15kg and 15 to <25 kg

[12] The primary objective of PRINCE I and PRINCE II was to describe safety of Reyataz POU boosted with RTV highly active ARV therapy in pediatric patients. In both studies, subjects continue on the powder formulation through the end of the 48-weeke period (Stage 1) and then move into Stage 2 remaining on the powder formulation or capsule formulation until subjects are 18 years or until approval.

[13] PRINCE I subjects were mainly from Africa and PRINCEII subjects were evenly split between African and non-African sites.

respectively (see Table 4); virologic success (HIV RNA <400 copies/mL) was 75% and 86% respectively for the same weight bands.

***DAVP Clinical Reviewer Comment***: *The antiviral activity results from AI424397 [PRINCE I] for subjects ≥ 10 kg…[ ]…were consistent with the results obtained for other antiretroviral agents used in pediatric trials, including ATV capsules for subjects ≥ 6 years of age.*

Virologic success rate in PRINCE II was not consistent with prior results obtained in trials of other antiretroviral agents including ATV dosed as capsules (PACTG trial) or as the POU in PRINCE I. Antiviral activity for subjects weighing 10 to <15 kg was low according to the clinical reviewer. Virologic success (HIV RNA<50 copies/mL) at 48 weeks was achieved by 31% of patients weighing 10 to <15kg (see Table 4); virologic success was more consistent with results from PRINCE I when using the HIV RNA <400 copies/mL cutoff, with 62% achieving "success" for the 10 to <15 kg weight band.

***DAVP Clinical Reviewer Comment***: *Given the interim nature of the data, it is too early to conclude that ATV powder did not demonstrate the expected antiviral activity in AI424451 [Prince II].*

**Table 4: Virologic Success Rates for PRINCE I and PRINCE II**

| | **Prince I Study** | | | **Prince II Study** | | |
|---|---|---|---|---|---|---|
| Baseline weight | 5 to <10kg | 10 to <15kg | 15 to <25kg | 5 to <10kg | 10 to <15kg | 15 to <25kg |
| Number (N) in cohort | 21 | 19 | 14 | 17 | 13 | 19 |
| **Virologic Success (HIV RNA <50 c/mL)** | 10 (48%) | 13 (68%) | 10 (71%) | 8 (47%) | 4 (31%) | 14 (74%) |

### 3.2 SAFETY

Clinical safety based on the known safety profile of Reyataz capsule formulation for use in pediatric patients (age 6 to less than 18 years), is derived from clinical exposure in the PACTG study. Additional assessment of safety in the aforementioned pediatric population is based on post-marketing safety data including serious advents events reported through the FDA Adverse Event Reporting System (FAERS) database.

A review of FAERS cases (July 8, 2009 - May 31, 2013) with Reyataz or atazanavir products identified 17 pediatric reports with a serious outcome,[14] including eight reports of liver abnormalities, one metabolic event and one cardiac event. No pediatric deaths were reported in FAERS during this timeframe.

Labeled safety information for Reyataz is highlighted in Table 5. No treatment-related deaths were reported in the PRINCEI and PRINCE II pediatric studies and according to

[14] Pediatric Postmarket Pharmacovigilance and Drug Utilization Review (S. Cotter and T. Ready), dated November 15, 2013.

the DAVP clinical reviewer, no new safety concerns were identified to warrant additions to safety information in the labeling for Reyataz POU.

***DAVP Clinical Reviewer Comment***: *The safety findings for AI424397 [PRINCE I] and AI424451 [PRINCE II] are very similar to the findings from the AI424020 capsule formulation cohort [PACTG study] (age 6 years to less than 18 years) reviewed previously, with the exception of fewer Grade 3-4 total bilirubin abnormalities (12% reported in AI424397and AI424451 overall compared to 58% in AI424020). The decreased incidence of Grade 3-4 hyperbilirubinemia may be related to the use of optimized ATV dosing in AI424397and AI424451 in comparison to the aggressive dose finding in AI424020 which resulted in some of the older subjects (> 6 years of age) receiving supratherapeutic doses of ATV (with elevated Cmax) especially in the cohorts that received unboosted ATV.*

**Table 5: Highlights of Labeled Safety Information for Reyataz®**

| Section | Reyataz®(atazanavir sulfate) capsules (label approved August 2013) |
|---|---|
| **CONTRAINDICATIONS** | • REYATAZ is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.<br>• Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John's wort, and sildenafil when dosed as REVATIO®. |
| **WARNINGS AND PRECAUTIONS** | • *Cardiac conduction abnormalities:* PR interval prolongation may occur in some patients. Use with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval.<br>• *Rash:* Discontinue if severe rash develops.<br>• *Hyperbilirubinemia:* Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. Do not dose reduce. If a concomitant transaminase increase occurs, evaluate for alternative etiologies.<br>• *Hepatotoxicity:* REYATAZ should be used with caution in patients with hepatic impairment. Patients with hepatitis B or C infection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment.<br>• *Nephrolithiasis and cholelithiasis* have been reported. Consider temporary interruption or discontinuation.<br>• Patients receiving REYATAZ may develop new onset or exacerbations of diabetes mellitus/hyperglycemia, immune reconstitution syndrome, and redistribution/accumulation of body fat.<br>• *Hemophilia:* Spontaneous bleeding may occur and additional factor VIII may be required. |

| | |
|---|---|
| **ADVERSE REACTIONS** | Most common adverse reactions (≥2%) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever. |
| **USE IN SPECIAL POPULATIONS** | • *Pregnancy:* Use only if the potential benefit justifies the potential risk.<br>• *Nursing mothers* should be instructed not to breastfeed due to the potential for postnatal HIV transmission.<br>• *Hepatitis B or C co-infection:* Monitor liver enzymes.<br>• *Renal impairment:* Do not use in treatment-experienced patients with end stage renal disease managed with hemodialysis.<br>• *Hepatic impairment:* REYATAZ should be used with caution in patients with mild to moderate hepatic impairment. Do not use REYATAZ in patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended. |

## 4 DISCUSSION

Reyataz POU has demonstrated clinical benefit in the treatment of HIV-1 infection in pediatric patients 3 months and older weighing at least 10 kg. The risks with Reyataz POU are consistent with the recognized risk for the approved capsule formulation, and according to the DAVP clinical reviewer, "product labeling for safety is appropriate with Warnings for cardiac conduction abnormalities, rash, Immune Reconstitution Syndrome, hepatotoxicity, cholelithiasis, and nephrolithiasis." There were no new safety findings in the PRINCE I and PRINCE II studies to warrant a REMS.

## 5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Reyataz (atazanavir) powder for oral use, Reyataz POU has demonstrated efficacy in the treatment of HIV-1 infection in pediatric patients 3 months and older weighing at least 10 kg. There were no new safety signals identified during the review of the application that required mitigation beyond labeling. Thus, the benefit-risk profile for Reyataz POU is acceptable and the risks can be mitigated through professional labeling.

Should DAVP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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