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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name: Reyataz® (atazanavir)

Pediatric Labeling Approval Dates: 02-Jun-2014 and 24-Sep-2015

Application Type/Number: NDA 21567 (capsule, oral), NDA 206352 (powder, oral)

Applicant/Sponsor: Bristol-Meyers Squibb

OSE RCM #: 2017-335

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Reyataz® (atazanavir) in pediatric patients.

Drug utilization patterns were assessed to capture pediatric use of atazanavir containing products (Reyataz® and Evotaz®) and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) from March 2013 to February 2017, annually. In the year ending in February 2017, a nationally estimated number of 35,567 unique patients received a dispensed prescription for Reyataz from U.S. outpatient retail pharmacies, of which the pediatric population aged 0-16 years accounted for 0.8% (270 patients). For the same time period, an estimated 5,536 unique patients received a dispensed prescription for Evotaz, of which the pediatric population aged 0-16 years accounted for less than 0.7% (40 patients). Although there appears to be some off-label use of Evotaz in pediatric patients younger than 17 years old, the use was very low.

This review was prompted by pediatric labeling changes approved on 02-Jun-2014 and 24-Sep-2015. On 02-Jun-2014, atazanavir oral powder was approved which expanded the indication for the treatment of HIV-1 infection to pediatric patients 3 months and older weighing between 10kg to less than 25kg. Previously, the capsule was approved in pediatric patients 6 years and older. Pediatric labeling changes on 24-Sep-2015 further expanded the indication for oral powder to patients 3 months and older weighing 5kg to less than 10kg and to patients 3 months and older weighing > 25kg.

DPV identified seven FAERS cases coded with serious outcomes in pediatric patients received from 31-May-2013 (FAERS cutoff date from last pediatric review) to 28-Feb-2017, and this small number is consistent with low domestic use in pediatric patients compared to all ages. Low use may decrease the voluntary reporting of any adverse event. No use outside the approved indication was identified in these reports.

Of the seven pediatric adverse event cases, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and no deaths directly associated with atazanavir treatment. Two disease-related deaths were reported.

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time. We recommend routine pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Reyataz (atazanavir) is an HIV-1 protease inhibitor and was first approved in 2003. Atazanavir is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection for patients 3 months and older weighing at least 5kg.

Atazanavir is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus.

Atazanavir has been presented to the pediatric advisory committee (PAC) in December 2009 and April 2014. Both PACs recommended returning to standard, ongoing monitoring for adverse events.

This review was prompted by pediatric labeling changes approved on 02-Jun-2014 and 24-Sep-2015.

02-Jun-2014 pediatric labeling change: Atazanavir oral powder was approved for use in pediatric patients at least 3 months and weighing between 10kg to less than 25kg. Previously, the capsule was approved in pediatric patients 6 years and older.

24-Sep-2015 pediatric labeling change: Expanded indication for oral powder to patients 3 months and older weighing 5kg to less than 10kg and to those weighing > 25kg.

- Formulations:

Oral capsules: Atazanavir is administered orally and is supplied as capsules in three dose strengths: 150mg, 200mg, and 300mg.

Oral powder: Atazanavir is also supplied as an oral powder packet containing 50mg atazanavir equivalent to 56.9mg of atazanavir sulfate.

- Dosing:

Atazanavir capsule dosage for pediatric patients (6 to less than 18 years of age) is based on body weight not to exceed the adult dose and must be taken with food. Atazanavir capsules without ritonavir are not recommended for treatment-experienced adult or pediatric patients with prior virologic failure.

Atazanavir oral powder for pediatric patients (at least 3 months of age and weighing at least 5kg) is based on body weight, must be taken with ritonavir (to boost atazanavir plasma levels) and food and should not be used in pediatric patients who weigh less than 5kg.

- Clinical Trials in Pediatric Patients:

The safety, pharmacokinetic profile, and virologic response of atazanavir in pediatric patients at least 3 months of age and older weighing at least 5kg were established in three open-label, multicenter clinical trials: PACTG 1020A (capsules), AI424-451 (oral powder), and AI424-397 (oral powder).

The safety profile in pediatric patients was generally similar to that observed in adults.

Pediatric trials with atazanavir capsules

- PACTG 1020A: In pediatric patients from 6 years to 21 years of age.

In this study, 105 patients 6 to less than 18 years of age (43 antiretroviral-naive and 62 antiretroviral-experienced) received once daily atazanavir capsule formulation, with or without ritonavir, in combination with two nucleoside reverse transcriptase inhibitors (NRTIs).

One-hundred five (105) patients (6 to less than 18 years of age) treated with the atazanavir capsule formulation, with or without ritonavir, were evaluated. Using an Intention to Treat (ITT) analysis, the overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <400 copies/mL at Week 96 were 51% (22/43) and 34% (21/62), respectively. The overall proportions of antiretroviral-naive and -experienced patients with HIV RNA <50 copies/mL at Week 96 were 47% (20/43) and 24% (15/62), respectively. The median increase from baseline in absolute CD4 count at 96 weeks of therapy was 335 cells/mm³ in antiretroviral-naive patients and 220 cells/mm³ in antiretroviral-experienced patients.

Adverse Reactions: The safety profile of atazanavir in pediatric patients (6 to less than 18 years of age) taking the capsule formulation was generally similar to that observed in clinical studies of atazanavir in adults. The most common Grade 2–4 adverse events ($\geq 5\%$, regardless of causality) reported in pediatric patients were cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%). Asymptomatic second-degree atrioventricular block was reported in <2% of patients. The most common Grade 3–4 laboratory abnormalities occurring in pediatric patients taking the capsule formulation were elevation of total bilirubin (≥ 3.2 mg/dL, 58%), neutropenia (9%), and hypoglycemia (4%). All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

Pediatric trials with atazanavir oral powder

- AI424-397 (PRINCE I): In pediatric patients from 3 months to less than 6 years of age
- AI424-451 (PRINCE II): In pediatric patients from 3 months to less than 11 years of age

In these studies 155 patients (59 antiretroviral-naive and 96 antiretroviral-experienced) received once daily atazanavir oral powder and ritonavir, in combination with two NRTIs. Patients 5kg to less than 10kg received either 150 mg or 200 mg atazanavir and 80 mg ritonavir oral solution; patients 10kg to less than 15kg received 200 mg atazanavir and 80 mg ritonavir oral solution; patients 15kg to less than 25kg received 250 mg atazanavir and 80 mg ritonavir oral solution; and patients 25kg to less than 35kg received 300 mg atazanavir and 100 mg ritonavir.

One hundred thirty-four (134) patients from both studies weighing 5kg to less than 35kg treated with atazanavir oral powder with ritonavir were evaluated. Using a modified ITT analysis, the overall proportions of antiretroviral-naive and antiretroviral-experienced patients with HIV RNA <400 copies/mL at Week 48 were 79% (41/52) and 62% (51/82), respectively in patients who received atazanavir oral powder with ritonavir. The overall proportions of antiretroviral-naive and antiretroviral-experienced patients with HIV RNA <50 copies/mL at Week 48 were 54% (28/52) and 50% (41/82), respectively in patients who received atazanavir oral powder with ritonavir. The median increase from baseline in absolute CD4 count (percent) at 48 weeks of therapy (last observation carried forward) was 215 cells/mm³ (6%) in antiretroviral-naive patients and 133 cells/mm³ (4%) in antiretroviral-experienced patients who received atazanavir oral powder with ritonavir.

Adverse Reactions: The safety profile of atazanavir in pediatric patients taking atazanavir oral powder was generally similar to that observed in clinical studies of atazanavir in pediatric patients taking atazanavir capsules. The most common Grade 3–4 laboratory abnormalities occurring in pediatric patients weighing 5kg to less than 35kg taking atazanavir oral powder were increased amylase (33%), neutropenia (9%), increased SGPT/ALT (9%), elevation of total bilirubin (≥ 2.6 times ULN, 16%), and increased lipase (8%). All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The Reyataz USPI¹ includes the following information under **Highlights**:

-----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.
- Coadministration with alfuzosin, triazolam, orally administered midazolam, ergot derivatives, rifampin, irinotecan, lurasidone (if REYATAZ is coadministered with ritonavir), lovastatin, simvastatin, indinavir, cisapride, pimozide, St. John's wort, nevirapine, and sildenafil when dosed as REVATIO®.

-----**WARNINGS AND PRECAUTIONS**-----

- *Cardiac conduction abnormalities:* PR interval prolongation may occur in some patients. ECG monitoring should be considered in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval.
- *Severe Skin Reactions:* Discontinue if severe rash develops.
- *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.
- *Phenylketonuria:* REYATAZ oral powder contains phenylalanine which can be harmful to patients with phenylketonuria.
- *Hepatotoxicity:* 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.
- *Nephrolithiasis and cholelithiasis* have been reported. Consider temporary interruption or discontinuation.
- The concomitant use of REYATAZ/ritonavir and certain other medications may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions.
- Patients receiving REYATAZ may develop new onset or exacerbations of diabetes mellitus/hyperglycemia, immune reconstitution syndrome, and redistribution/accumulation of body fat.
- *Hemophilia:* Spontaneous bleeding may occur and additional factor VIII may be required.

-----**ADVERSE REACTIONS**-----

- Most common adverse reactions ($\geq 2\%$) are nausea, jaundice/scleral icterus, rash, headache, abdominal pain, vomiting, insomnia, peripheral neurologic symptoms, dizziness, myalgia, diarrhea, depression, and fever.

-----**DRUG INTERACTIONS**-----

- Coadministration of REYATAZ can alter the concentration of other drugs and other drugs may alter the concentration of atazanavir. The potential drug-drug interactions must be considered prior to and during therapy.

-----**USE IN SPECIFIC POPULATIONS**-----

- *Pregnancy:* Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate.
- *Lactation:* Breastfeeding is not recommended.
- *Hepatitis B or C co-infection:* Monitor liver enzymes.
- *Renal impairment:* REYATAZ is not recommended for use in treatment-experienced patients with end stage renal disease managed with hemodialysis.

- *Hepatic impairment:* REYATAZ is not recommended in patients with severe hepatic impairment. REYATAZ/ritonavir is not recommended in patients with any degree of hepatic impairment.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the FDA to conduct this analysis.

Appendix A includes detailed descriptions of the databases.

2.1.1 Data Sources Used

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various retail and non-retail U.S. channels of distribution for Reyataz and Evotaz in 2016.

The IMS Health, Total Patient Tracker™ database was used to obtain the nationally estimated number of unique patients who received dispensed prescriptions for Reyataz and Evotaz from U.S. outpatient retail pharmacies, stratified by patient age groups (<1, 1-5, 6-12, 13-16, and 17 years and older) from March 2013 through February, 2017, annually.

2.2 RESULTS

2.2.1 Determining Settings of Care

In 2016, approximately 54% of Reyataz bottles/packages were distributed to U.S. outpatient retail pharmacies, followed by 25% to non-retail and 21% to mail order/specialty pharmacy settings.^a In 2016, approximately 62% of Evotaz bottles were sold to U.S. outpatient retail pharmacies, followed by 21% to non-retail and 17% to mail order/specialty pharmacy settings. Based on these results, we examined the drug utilization data for only the U.S. outpatient retail settings.^b

^a QuintilesIMS, National Sales Perspective.™ Year 2016. Extracted May 2016. File: NSP- Atazanavir BPCA (Reyataz and Evotaz) year 2016. 05.11.2017.xlsx

2.2.2 Number of Patients

Table 1. Nationally estimated number of unique patients with a dispensed prescription for Reyataz (atazanavir) and/or Evotaz (atazanavir/cobicistat) stratified by patient age*, from U.S. outpatient retail pharmacies, March 2013 through February 2017, annually

	March 2013-Feb 2014		March 2014-Feb 2015		March 2015-Feb 2016		March 2016-Feb 2017	
	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)	Patient (N)	Share (%)
Total Reyataz	72,220	100.0%	63,101	100.0%	50,618	100.0%	35,567	100.0%
0 - 16 years	450	0.6%	632	1.0%	386	0.8%	270	0.8%
<1 years	1	0.3%	1	0.1%	1	0.2%	--	--
1 - 5 years	8	1.8%	18	2.9%	8	2.1%	6	2.4%
6 - 11 years	96	21.3%	174	27.6%	128	33.1%	115	42.5%
12 - 16 years	353	78.3%	378	59.8%	230	59.6%	159	58.8%
17+ years	71,200	98.6%	62,129	98.5%	50,258	99.3%	35,318	99.3%
Unknown Age	4,491	6.2%	2,618	4.1%	537	1.1%	65	0.2%
Total Evotaz	--	--	103	100.0%	3,896	100.0%	5,536	100.0%
0 - 16 years	--	--	--	--	29	0.7%	40	0.7%
<1 years	--	--	--	--	--	--	--	--
1 - 5 years	--	--	--	--	--	--	--	--
6 - 11 years	--	--	--	--	2	7.0%	3	8.6%
12 - 16 years	--	--	--	--	25	87.2%	31	77.2%
17+ years	--	--	103	100.0%	3882	99.7%	5,523	99.8%
Unknown Age	--	--	--	--	6	0.2%	2	<0.1%

* Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months old)

** Unique patient count may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in individual categories.

***Although there appears to be some off-label use of Evotaz in pediatric patients younger than 17 year old, the patient count is very low and may be due to error. This use cannot be validated due to the lack of access to patient medical records.

Source: QuintilesIMS, Total Patient Tracker™ Years March 2007- March 2017 Data Extracted May 2017 File: TPT-Reyataz-Evotaz-MAT- 2013-2017. 05.10.2017.xlsx

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FAERS Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	13-Mar-2017
Time Period of Search	31-May-2013* to 28-Feb-2017
Search Type	FBIS Quick Query, Product-Manufacturer Reporting Summary

Table 3.1.1 FAERS Search Strategy

Product Names:	Reyataz; atazanavir sulfate; atazanavir/ritonavir; atazanavir sulfate/ritonavir; atazanavir/lamivudine/ritonavir/zidovudine; atazanavir
Product Active Ingredient:	Atazanavir sulfate; atazanavir/ritonavir; atazanavir sulfate/cobicistat; atazanavir sulfate/ritonavir; atazanavir/lamivudine/ritonavir/zidovudine; atazanavir
Active Ingredient:	Atazanavir sulfate; atazanavir

Search Parameters	All ages, all outcomes, worldwide
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** FAERS cutoff date from last pediatric review completed in Nov 2013*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* 31-May-2013 to 28-Feb-2017 with Atazanavir

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	1625 (493)	1492 (365)	74 (26)
Pediatrics (0 - <17 years)	143 (84)	140[‡] (81)	13 [§] (8)

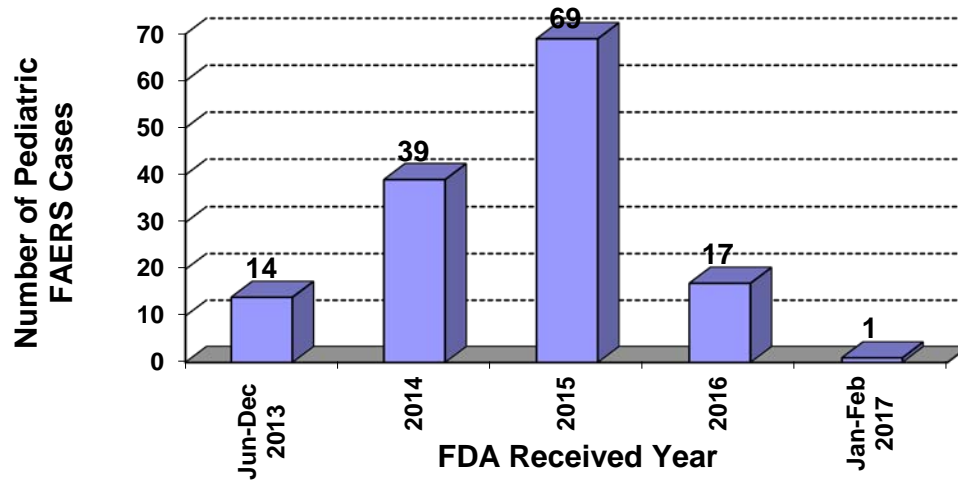
** May include duplicates and transplacental exposures, and have not been assessed for causality*

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 3.2.2

§ One additional report of pediatric death was identified among reports not reporting an age.

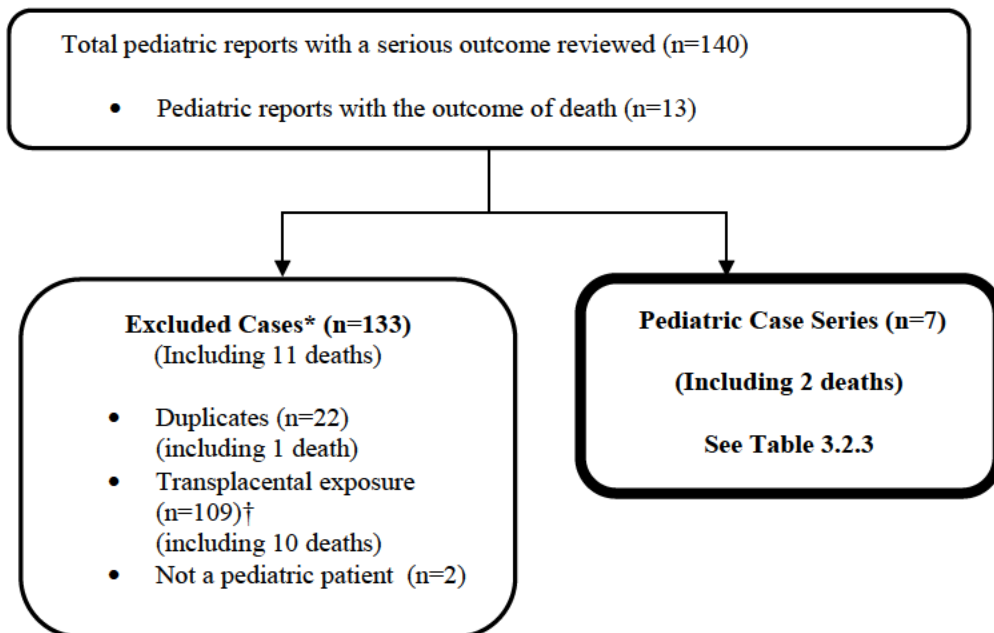
Figure 3.2.1 Serious Pediatric Reports for Atazanavir, by year of FDA receipt 31-May-2013 to 28-Feb-2017 (n=140)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 140 pediatric reports with a serious outcome (Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4**.

Figure 3.2.2 Selection of Serious Pediatric Cases with Atazanavir



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.

† Transplacental exposure cases include reports from the Antiretroviral Pregnancy Registry (APR). The APR was established in 1989 to provide an early signal of any major teratogenic effect associated with a prenatal exposure to antiretroviral drugs. The APR is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. Sponsors of all antiretroviral agents, including atazanavir, participate in the registry upon approval. The scientific conduct and analysis of the APR are overseen by an advisory committee consisting of members from the Centers for Disease Control and Prevention (CDC), FDA, the National Institutes of Health (NIH), as well as the private sector.

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Atazanavir (n=7)

Age (n=6)	0 - < 1 month	0
	1 month - <2 years	0
	2- < 6 years	0
	6- <12 years	3
	12- < 17 years	3
Sex	Male	2
	Female	4
	Unknown	1
Country	United States	4
	Foreign	3
Reported Reason for Use	HIV infection	6
	Unknown	1
Serious Outcome*	Death	2
	Hospitalization	1
	Disability	1
	Other serious	3

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

A total of two cases reported death as an outcome. No deaths were directly associated with atazanavir. Both deaths were disease-related.

One death (derived from “null” age death reports) was a study literature report from “The European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord” which investigated the real life use and long term safety of darunavir and atazanavir in children enrolled in observational cohorts.² A pediatric patient of unknown age, gender and ethnic origin received lamivudine, tenofovir, emtricitabine, abacavir, ritonavir, lopinavir, darunavir and atazanavir (therapy dates, doses were not reported). The report contained very little information (medical history, concomitant medications were not reported) and the death was described as “AIDS-related” (FAERS case #11784538-1, Great Britain).

The second death was from a literature report describing cases of HIV genotype resistance testing in antiretroviral exposed Indian children. The death was due to HIV. The patient had drug resistance to multiple antiretrovirals and possible resistance to atazanavir. It is unclear from the narrative if the patient had ever received treatment with atazanavir, but because it reported possible drug resistance to atazanavir, it was included in the case series for completeness. The case is summarized below:

FAERS case # 9349255-2, India, literature case report ³:

A 10-year-old male with HIV infection was treated since approximately 5 years of age with antiretroviral therapy that included zidovudine and nevirapine, followed by stavudine, lamivudine and efavirenz. At approximately 7 years of age, he was switched to didanosine, abacavir and lopinavir+ritonavir therapy. Approximately two years later, his HIV viral load was 1,800,000 copies per ml and CD4 cell count was 61 cells/mm³ (11.47%). He presented with wasting (weight 15kg), facial molluscum contagiosum and oral thrush. HIV genotype resistance testing (GRT) showed resistance to multiple antiretrovirals including possible resistance to atazanavir. His antiretroviral therapy was changed to abacavir, lamivudine, and lopinavir+ritonavir. Six months later, his HIV viral load was 73,200 copies per mL and abdomen ultrasonography showed mesenteric lymph nodes with mesenteric thickening. He was started on four anti-tuberculous therapy drugs (rifabutin based) and antiretroviral therapy continued. Four months later, his HIV viral load was undetectable but CD4 cell count was 10 cells/mm³. Six months later his weight decreased to 14kg. HIV viral load and CD4 cell count were not reported. Repeat GRT several months later showed M184V mutation conferring lamivudine resistance. The patient subsequently succumbed to his illness.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=5)

Five non-fatal adverse event cases in pediatric patients were evaluated. DPV did not identify potential new risks, or known/labeled risk reported in unusual numbers in pediatric patients. No use outside the approved indication was identified.

3.4.1 Labeled Events: (n=5)

The five cases reported labeled events. Two of the five cases reported increased bilirubin which is consistent with the known risk in the labeling under Warnings and Precautions and no increased severity was observed in these reports. The third case was a literature case report of a drug-drug interaction between atazanavir+ritonavir and inhaled corticosteroids which is consistent with the known risk in the labeling under Drug Interactions and no increased severity was observed in the report. The fourth case reported decreased appetite, malaise, and vomiting. Vomiting is labeled under Adverse Reactions. The fifth case reported bloody vomiting, ocular icterus, and yellow skin. Ocular icterus, yellow skin and vomiting are labeled, but the events in this case have an unclear etiology and there is insufficient information to make a causal assessment.

All five cases are summarized below:

Labeled event –Blood bilirubin increased, ocular icterus (n=1):

FAERS case #10379229-2, USA:

A six-year-old female patient began therapy with atazanavir 200 mg orally and ritonavir at a daily dose of 100 mg daily for the treatment of HIV infection. Approximately 7 weeks later, the patient had yellowing of eyes with hyperbilirubinemia of 4.8 mg/dl, otherwise she was asymptomatic. She was under observation and on an unspecified date, yellowing of eyes spontaneously resolved with change in dose of medications. At the time of this report, atazanavir therapy was ongoing.

Laboratory test results included the following: Approximately 3 months after beginning atazanavir: serum bilirubin 4.5 mg/dl (normal: 0.2-1.2), aspartate transaminase (AST) 30 u/l (normal: 15-50), alanine aminotransferase (ALT) 18 u/l (normal: 10-25), alkaline phosphatase 396 u/l (normal: 150-380), albumin 4 g/dl (normal: 3.8-5.4) and bicarbonate 21 millimole/l (normal: 16-26). Approximately six weeks prior to beginning atazanavir: bilirubin 0.5mg/dl, AST 41 u/l, ALT 29 u/l, alkaline phosphatase 361 u/l, albumin 4.3 and bicarbonate 24 millimole/l.

Reviewer comment: The events are consistent with the known risk in the labeling. Under Warnings and Precautions the label states “Most patients taking Reyataz experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT). This hyperbilirubinemia is reversible upon discontinuation of atazanavir. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies.” The label also states that alternative antiretroviral therapy to atazanavir may be considered if jaundice or conjunctival icterus associated with bilirubin elevations presents cosmetic concerns for patients. This patient had normal transaminases; therefore, based on the label, no additional work up was needed.

Labeled event –Blood bilirubin increased, ocular icterus, yellow skin (n=1):

FAERS case #9713766-1, USA:

A 16-year-old male patient began therapy with atazanavir 300 mg daily for HIV infection. About 5-6 days later, he noticed yellowing of his eyes and palms. His total bilirubin was elevated at 7.9 (units not reported) as well. He did not have any nausea, vomiting, or diarrhea. The patient did not take any new prescriptions, over the counter medications, or supplements during this time. Other “liver function labs” were within normal limits and he was also tested for hepatitis A, B, and C and he was found to be negative for all. Atazanavir was discontinued and a week later, the yellowing of his eyes and palms resolved.

Reviewer comment: The events are consistent with the known risk in the labeling. See comments above for FAERS case #10379229-2. This patient had normal liver function tests (transaminases); therefore, based on the label, no additional work up was needed.

Labeled event –Cushingoid, drug interaction, hirsutism, skin striae, weight increased (n=1):

FAERS case #10480604-1, USA, literature case report ⁴:

A 14-year-old female patient experienced weight gain, striae, cushingoid facies, and facial hirsutism following two weeks of concomitant usage of tenofovir disoproxil fumarate, ritonavir 100mg, atazanavir, didanosine, inhaled fluticasone propionate, salmeterol and montelukast. The patient was hospitalized for adrenal insufficiency (note: hospitalization was not coded in FAERS report). Atazanavir, ritonavir and fluticasone propionate were discontinued. The symptoms resolved after dechallenge.

Reviewer comment: The events of cushingoid facies, facial hirsutism, skin striae, and weight increased are signs of systemic corticosteroid effects. The events are consistent with the known risk in the labeling for systemic corticosteroid effects due to concomitant use of inhaled corticosteroids and atazanavir/ritonavir. Under Drug Interactions the label states, “Concomitant use of fluticasone propionate and atazanavir/ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations.” The label also states, “Systemic corticosteroid effects, including Cushing’s syndrome and adrenal suppression, have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Coadministration of fluticasone propionate and REYATAZ/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect.”

Labeled event - Decreased appetite, malaise, vomiting (n=1):

FAERS case #10576740-1, USA:

A parent reported that her 9-year-old daughter was feeling sick. She would vomit and had a loss of appetite. The patient’s physician switched her from atazanavir to efavirenz. Concomitant medications were not reported. Outcome was not reported. The events were assessed as involving persistence or significant disability or incapacity.

Reviewer comment: Vomiting is labeled under Adverse Reactions-Clinical Trials Experience (for both adult and pediatric clinical trial patients). Malaise and decreased appetite are not labeled. The events may have been due to unreported concomitant

medications that the patient was likely taking given the standard of combination antiretroviral therapy for HIV.

Labeled event – Haematemesis, ocular icterus, yellow skin (n=1):

FAERS case #12922932-1, Brazil:

A 14-year-old female began therapy with atazanavir at a dose of 300 mg 1 tablet a day, tenofovir + lamivudine and ritonavir (unknown dose and frequency) for HIV infection. The patient's parent reported that after one week of starting treatment, the patient experienced bloody vomiting, which always happened about 2 hours after taking medication at night (the patient did not experience many episodes of vomiting during the day, only one at night and the throat of the patient was not injured nor inflamed). On an unknown date the patient experienced yellowish eyes and skin. It was reported that about four months ago, the patient was treated with valproic acid, haloperidol, amitriptyline and clonazepam (therapy dates not reported). The patient was under treatment with a psychiatrist. The patient received valproic acid along with antiretrovirals. The action taken with the therapy in response to the event was unknown and outcome of the events bloody vomiting, yellowish eyes and yellowish skin was not resolved.

Reviewer comment: Ocular (more accurately, conjunctival) icterus, and yellow skin are labeled under Warnings and Precautions. Haematemesis is not labeled but vomiting is labeled under Adverse Reactions-Clinical Trials Experience (for both adult and pediatric clinical trial patients). The events in this case have an unclear etiology and there is insufficient information (such as transaminase test results) to make a causal assessment. The patient was treated concomitantly with valproic acid which has a Boxed Warning for hepatotoxicity. Valproic acid is also labeled for hematemesis and vomiting under Adverse Reactions.⁵

4 DISCUSSION

Analysis of the drug utilization data during the 12-month period ending in February 2017 showed that pediatric patients aged 0-16 years old accounted for less than 1% of total patients who received a dispensed prescription for Reyataz and/or Evotaz from U.S. outpatient retail pharmacies. Within the pediatric age group, the vast majority of use was among children 12-16 years old, followed by 6-11 years. Of note, Reyataz oral powder is approved for use in treatment-naive or treatment-experienced pediatric patients who are at least 3 months of age and weighing at least 5 kg.

During the examined time period, annual nationally estimated number of total patients and pediatric patients aged 12-16 years who received a dispensed prescription for Reyataz decreased by 50% and 25%, respectively. Although there appears to be some off-label use of Evotaz in

patients 6-16 years, this use cannot be validated due to the lack of access to patient medical records. We focused our analyses on the outpatient retail pharmacy setting only where the largest proportion of atazanavir-containing products was distributed. However, because HIV medications may be dispensed from HIV clinics and other settings not captured in this analysis, it is important to note that these estimates may not be representative of all treatment for HIV in the U.S. and may underestimate the total utilization.

DPV included seven FAERS cases in pediatric patients in the case series, and this small number is consistent with low domestic use in pediatric patients compared to all ages. Low use may decrease the voluntary reporting of any adverse event. No use outside the approved indication was identified in these reports.

Of the seven pediatric adverse event cases, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and no deaths directly associated with atazanavir. Two disease-related deaths were reported.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

6 RECOMMENDATIONS

DPV recommends routine pharmacovigilance monitoring.

7 REFERENCES

1. Reyataz® [package insert]. Princeton, NJ: Bristol-Meyers Squibb Company; 2017.
2. Judd A, Bailey H, Jeannie I, et al. Safety of darunavir and atazanavir in HIV-infected children in Europe and Thailand. *Antiviral Therapy* 2016; 21:353-358.
3. Shah I, Parikh S. HIV genotype resistance testing in antiretroviral (ART) exposed Indian children - A need of the hour. *Indian Journal of Pediatrics* 2013;80:340-2.
4. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Medicine* 2013; 14: 519-529.
5. Depakene [package insert]. North Chicago, IL: AbbVie; 2017.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

QuintilesIMS, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, Total Patient Tracker™ (TPT)

QuintilesIMS, Total Patient Tracker™ (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH ATAZANAVIR (N=7)

FAERS case-version numbers and manufacturer control numbers included in pediatric case series (n=7)		
Ref #	FAERS case-version #	Mfr#
1	9349255-2	IN-BRISTOL-MYERS SQUIBB COMPANY-18979351
2	9713766-1	Not applicable - Direct report
3	10379229-2	US-BRISTOL-MYERS SQUIBB COMPANY-19193911
4	10480604-1	2014HINLIT0830
5	10576740-1	US-BRISTOL-MYERS SQUIBB COMPANY-21552435
6	11784538-1	GB-CIPLA LTD.-2015GB08934
7	12922932-1	BR-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-093562

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAULA L GISH
06/22/2017

NABILA SADIQ
06/22/2017
Drug Use Data cleared on 06/21/2017

SUSAN J BERSOFF-MATCHA
06/22/2017

JUSTIN A MATHEW
06/22/2017

KELLY Y CAO
06/23/2017

GRACE CHAI
06/23/2017

IDA-LINA DIAK
06/23/2017