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Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets, for oral use)
Pediatric Labeling Approval Date:	March 28, 2013
Application Type/Number:	NDA 204061
Applicant/Sponsor:	Teva Women's Health, Inc.
OSE RCM #:	2016-1206

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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 and drug utilization data for Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets, for oral use) in pediatric patients.

Quartette was first approved in 2013 and is indicated for use by females of reproductive age to prevent pregnancy. Safety and efficacy of Quartette have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of Quartette before menarche is not indicated.

From March 2013 through May 2016, a nationally estimated number of approximately 32,000 patients received a dispensed prescription for Quartette from U.S. outpatient retail pharmacies. Out of 32,000 patients, pediatric population aged 0-17 years, accounted for 11% (3,571 patients) of total patients.

Pediatric FAERS reports from March 28, 2013, to May 24, 2016, were reviewed to assist in the identification of rare, serious, or unlabeled adverse events related to the use of Quartette in the pediatric population. The search retrieved one pediatric case; no deaths were reported. Review of this case did not identify any new safety signals or an increase in the severity or frequency of any labeled adverse event.

Based on this review, there is no evidence from this data that there are pediatric safety concerns with Quartette at this time. DPV recommends returning to routine pharmacovigilance monitoring for Quartette.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets, for oral use) is an estrogen/progestin combination oral contraceptive (COC). Quartette is a 91-day course COC which is taken in the following order:[1]

1. 0.15 mg of levonorgestrel and 0.02 mg of ethinyl estradiol (light pink tablet) taken once daily for 42 consecutive days.
2. 0.15 mg of levonorgestrel and 0.025 mg of ethinyl estradiol (pink tablet) taken once daily for 21 consecutive days.
3. 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol (purple tablet) taken once daily for 21 consecutive days.
4. 0.01 mg of ethinyl estradiol (yellow tablet) taken once daily for 7 consecutive days. Bleeding should occur during yellow tablet use.

Quartette was approved on March 28, 2013, and is indicated for use by females of reproductive age to prevent pregnancy. The Pediatric Review Committee (PeRC) of the FDA agreed to the Sponsor's requested partial waiver for premenarchal females and the extrapolation of adult data to postmenarchal adolescents.[2] The safety and efficacy of Quartette have been established in women of reproductive age, and are expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of Quartette before menarche is not indicated.[1]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The package insert contains the following information under the HIGHLIGHTS OF PRESCRIBING INFORMATION section:[1]

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- **Women over 35 years old who smoke should not use Quartette. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

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

- Vascular risks: Stop Quartette if a thrombotic event occurs. Stop Quartette at least 4 weeks before and through 2 weeks after major surgery. Start Quartette no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Quartette if jaundice occurs. (5.2)
- High blood pressure: Do not prescribe Quartette for women with uncontrolled hypertension or hypertension with vascular disease. (5.3)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Quartette. Consider an alternate contraceptive method for women with uncontrolled dyslipidemias. (5.5)
- Headache: Evaluate significant change in headaches and discontinue Quartette if indicated. (5.6)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 2%) in clinical trials for Quartette were headaches, heavy/irregular vaginal bleeding, nausea/vomiting, acne, dysmenorrhea, weight increased, mood changes, anxiety/panic attack, breast pain and migraines. (6)

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

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

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the Agency to conduct this analysis. **Appendix A** includes detailed descriptions of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ **(*NSP)*** database was used to determine the various settings of care where Quartette is distributed by the manufacturer. Sales distribution data for 2015 showed that approximately 91% of Quartette packages were sold to U.S. outpatient retail pharmacies, followed by 3% to non-retail settings and 6% to mail order/specialty pharmacy settings. Based on these results, we examined the drug utilization data for only the U.S. outpatient retail pharmacy settings.

2.1.2 Data Sources Used

The IMS Health, IMS Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for Quartette from U.S. outpatient retail pharmacies, stratified by patient age groups 0-11, 12-17 and 18+ years and older from March 2013 through May 2016, cumulative.

2.2 RESULTS

Nationally estimated number of unique patients who received a dispensed prescription for Quartette from U.S. outpatient retail pharmacies stratified by patient age*, March 2013- May 2016, cumulative

	March 2013- May 2016	
	Patients (N)	**Share (%)**
Total Quartette Patients	**31,845**	***100.0%***
0 - 17 years	**3,571**	**11%**
0-11 years	25	*0.7%*
12-17 years	3,551	*99.4%*
18+ years and older	**28,915**	***90.8%***
Unknown age	146	*0.5%*

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include <18 years of age (17 years and 11 months).
Source: IMS Total Patient Tracker. Years March 2013- May 2016 Data Extracted August 2016 File: 2016-1206-TPT-Quartette -BPCA-custom age- March 2013-May 2016. 08.09.2016.xls

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (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	May 24, 2016
Time Period of Search	March 28, 2013* - May 24, 2016
Search Type	Profile Report and Quick Query
Product Name	Product Name: Quartette

Table 3.1.1 FAERS Search Strategy	
Additional Criteria	NDA #: 204061
Search Parameters	All ages, all outcomes, worldwide

[*] *Date of U.S. approval*

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 Total Adult and pediatric FAERS reports* from March 28, 2013, to May 24, 2016, with Quartette

	All reports (US)	**Serious[†] (US)**	**Death (US)**
Adults (≥ 17 years)	17 (17)	4 (4)	0 (0)
Pediatrics (0 - <17 years)	1 (1)	0 (0)	0 (0)

** 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.

3.2.2 Selection of Pediatric Cases in FAERS

We identified one pediatric report and this case is summarized in **Section 3.4.**

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

No pediatric death cases were identified.

3.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=1)

The sole pediatric case is described in further detail below:

FAERS Case # 10226938/Manufacturer Control # US-TEVA-469618USA/Version 2, United States, Outcome – Non-serious, Reported MedDRA Preferred Term: Pain in Extremity A physician reported that a 15-year-old patient reported new onset leg cramps approximately nine days after the initiation of Quartette. The patient was advised to continue the medication, increase her hydration, and eat bananas. The plan was to discontinue Quartette if symptoms did not improve after one month. It was noted that the patient had a "negative past medical history and family history." Prior to the start of Quartette, the patient had been receiving Depo-Provera (medroxyprogesterone acetate for injection). Depo-Provera had been discontinued because of a 30 pound weight gain in eight months. The last Depo-Provera injection was approximately three months prior to the initiation of Quartette. No additional information regarding the outcome was provided.

Reviewer's Comments: This case did not provide sufficient details for an analysis of a drug-event association between Quartette and the patient's new onset leg cramps. Current Quartette labeling includes the terms 'muscle spasms' and 'pain in extremity' in section 6 ADVERSE REACTIONS, 6.2 POSTMARKETING EXPERIENCE.

4 DISCUSSION

Analysis of drug utilization data shows pediatric patients aged 0-17 years accounted for 11% of the total patients who received a dispensed prescription for Quartette from outpatient retail pharmacies. Among the pediatric patients, patients ages 12- 17 years accounted for over 99% of pediatric patients. Although <1% of pediatric patients were captured for ages 11 years or younger, medical chart validation was not available to verify this utilization.

Pediatric FAERS reports from March 28, 2013, to May 24, 2016, were reviewed to assist in the identification of rare, serious, or unlabeled adverse events related to the use of Quartette in the pediatric population.

The search retrieved one pediatric case; no deaths were reported. Review of this case did not identify any new safety signals or an increase in the severity or frequency of any labeled adverse event.

5 CONCLUSION

Based on this review, there is no evidence from this data that there are pediatric safety concerns with Quartette at this time.

6 RECOMMENDATIONS

OSE recommends returning to routine pharmacovigilance monitoring for Quartette.

7 REFERENCES

[1] Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets) [Package Insert]. North Wales, PA: Teva Women's Health, Inc.; May 2014.

[2] Popat V. NDA 204061; Clinical Review for Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets). March 3, 2013. Accessible at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM353848.pdf

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, 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.

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. Based on sales data for 2015, Quartette was primarily distributed to U.S. outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

IMS Vector One®: Total Patient Tracker (TPT)

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.

Findings from drug utilization should be interpreted in the context of the known limitations of the databases used. We estimated that Quartette was distributed primarily to the outpatient retail setting, based on the IMS Health, IMS National Sales Perspectives™ database. As such, we focused our analysis only on the outpatient retail pharmacy settings. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care in which these products may be used or dispensed.

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.

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