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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Names: Xeloda[®] (capecitabine)

**Pediatric Labeling
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EXECUTIVE SUMMARY

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

Capecitabine, a fluoropyrimidine carbamate with antineoplastic activity, was first approved in 1998 and is indicated for:

- **Adjuvant Colon Cancer**
 - Patients with Dukes' C colon cancer
- **Metastatic Colorectal Cancer**
 - First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred
- **Metastatic Breast Cancer**
 - In combination with docetaxel after failure of prior anthracycline-containing chemotherapy
 - As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

Capecitabine was not approved for a pediatric indication based on lack of efficacy in clinical trials.

In order to capture pediatric use of capecitabine and to provide context for the adverse event reports submitted to the Food and Drug Administration (FDA), drug utilization patterns were assessed. Sales distribution data from September 2011 through August 2015 show that the largest proportion of sales for capecitabine was to outpatient mail-order/specialty and retail pharmacies. Focusing on the outpatient setting of care, analyses of healthcare claims data from a sample of 17,614 outpatient pharmacies found approximately 99.9% (103,998 patients) of total patients with a prescription claim for capecitabine were adults aged 18 years and older. Pediatric patients aged 0-17 years accounted for less than 0.5% (36 patients) of the sample population. It should be noted, that the capecitabine drug utilization data presented in this review were obtained from a sample of outpatient pharmacies. These data are not nationally projected and nationwide pediatric projections for capecitabine were not available at the time of the review.

Sixteen adverse event cases in pediatric patients received from April 30, 1998 (drug approval date) and August 31, 2015 were evaluated. Two disease-related deaths and one fatal surgical complication were reported. The small number of reports is consistent with low use in pediatric patients due to lack of efficacy.

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

Capecitabine is a fluoropyrimidine carbamate nucleoside metabolic inhibitor with antineoplastic activity indicated for:

- **Adjuvant Colon Cancer**
 - Patients with Dukes' C colon cancer
- **Metastatic Colorectal Cancer**
 - First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred
- **Metastatic Breast Cancer**
 - In combination with docetaxel after failure of prior anthracycline-containing chemotherapy
 - As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

Capecitabine is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. Capecitabine is supplied in 150 and 500mg tablets.

This review was triggered by new information generated from two single arm trials in pediatric patients. The safety and effectiveness of capecitabine in pediatric patients was not established in these trials as no clinical benefit was demonstrated in pediatric patients with newly diagnosed brainstem gliomas and high grade gliomas. The adverse event profile of capecitabine was consistent with the known adverse reaction profile in adults, with the exception of laboratory abnormalities¹.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The package insert¹ contains the following information under **Highlights**:

WARNING: XELODA-WARFARIN INTERACTION SEE FULL PRESCRIBING INFORMATION FOR COMPLETE BOXED WARNING.

Patients receiving concomitant XELODA and oral coumarin-derivative anticoagulants such as warfarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported during concomitant use.

- Occurrence: Within several days and up to several months after initiating XELODA therapy; may also be seen within 1 month after stopping XELODA
- Predisposing factors: age>60 and diagnosis of cancer

----- **CONTRAINDICATIONS** -----

- Severe Renal Impairment
- Hypersensitivity

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

- **Coagulopathy:** May result in bleeding, death. Monitor anticoagulant response (e.g., INR) and adjust anticoagulant dose accordingly.
- **Diarrhea:** May be severe. Interrupt XELODA treatment immediately until diarrhea resolves or decreases to grade 1. Recommend standard antidiarrheal treatments.
- **Cardiotoxicity:** Common in patients with a prior history of coronary artery disease.
- **Increased Risk of Severe or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity:** Withhold or permanently discontinue XELODA in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe in patients with absent DPD activity.
- **Dehydration and Renal Failure:** Interrupt XELODA treatment until dehydration is corrected. Potential risk of acute renal failure secondary to dehydration. Monitor and correct dehydration.
- **Pregnancy:** Can cause fetal harm. Advise women of the potential risk to the fetus.
- **Mucocutaneous and Dermatologic Toxicity:** Severe mucocutaneous reactions, Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been reported. XELODA should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment. XELODA may induce hand-and-foot syndrome. Interrupt XELODA treatment until the hand-and-foot syndrome event resolves or decreases in intensity.
- **Hyperbilirubinemia:** Interrupt XELODA treatment immediately until the hyperbilirubinemia resolves or decreases in intensity.
- **Hematologic:** Do not treat patients with neutrophil counts $<1.5 \times 10^9/L$ or thrombocyte counts $<100 \times 10^9/L$. If grade 3-4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.

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

Most common adverse reactions ($\geq 30\%$) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Other adverse reactions, including serious adverse reactions, have been reported.

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

- **Anticoagulants:** Monitor anticoagulant response (INR or prothrombin time) frequently in order to adjust the anticoagulant dose as needed.
- **Phenytoin:** Monitor phenytoin levels in patients taking XELODA concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- **Leucovorin:** The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin.
- **CYP2C9 substrates:** Care should be exercised when XELODA is coadministered with CYP2C9 substrates.
- **Food:** reduced both the rate and extent of absorption of capecitabine.

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

- **Nursing Mothers:** Discontinue nursing when receiving XELODA treatment.
- **Geriatric:** Greater incidence of adverse reactions. Monitoring required.
- **Hepatic Impairment:** Monitoring is recommended in patients with mild to moderate hepatic impairment.
- **Renal Impairment:** Reduce XELODA starting dose in patients with moderate renal impairment.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary drug utilization databases were used to conduct this analysis. Detailed descriptions and limitations of the databases are included in Appendix A.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for Xeloda® (capecitabine) from September 2011 through August 2015. Sales data for capecitabine by the number of bottles sold from the manufacturer to all U.S. channels of distribution indicated that approximately 48% of capecitabine bottles were sold to mail order/specialty pharmacies, 26% to non-retail settings, and 26% to outpatient retail pharmacies.² Therefore, this drug utilization analysis focuses on capecitabine use according to prescription claims from outpatient pharmacies, including both retail and mail-order pharmacies.

2.1.2 Data Sources Used

The Symphony Health Solutions' Integrated Dataverse (IDV)™ database was used to obtain the number of unique patients with a pharmacy prescription claim for capecitabine, stratified by patient age (0-4 years, 5-17 years, and 18 years and older), from September 2011 through August 2015, aggregated. The data were restricted to this time period based on the data availability in the database. National pediatric projections of this data were not available at the time of the review and thus the data only represent a sample of 17,614 outpatient pharmacies.

Patient selection in Symphony Health Solutions' IDV was based on the presence of a prescription claim using National Drug Codes (NDCs) for capecitabine. Patients with a prescription claim for capecitabine were also stratified by prescriber specialties and selected diagnoses codes of interest. The selected diagnoses codes of interest were captured using the International Classification of Diseases, Ninth Revision System (ICD-9), only in patients with a diagnosis claim made within 180 days prior to or 180 days subsequent to an capecitabine prescription claim. The selected diagnoses codes of interest were grouped into the following indications: colon cancer, colorectal cancer, and breast cancer, brain cancer, esophageal cancer, gastric cancer, and pancreatic cancer. These diagnoses groups were selected to capture approved and unapproved indications for capecitabine. Study parameters with a complete list of the selected diagnoses codes and NDCs are included in Appendix B.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1 provides the total number of patients with a prescription claim for capecitabine captured from a sample of pharmacies, stratified by patient age, from September 2011 through August 2015, aggregated. During this time period, a total of 104,037 patients had a prescription claim for capecitabine. The vast majority of the patients were adults aged 18 years and older, accounting for approximately 99.9% (103,998 patients) of total patients. The pediatric population aged 0-17 years accounted for less than 0.5% (36 patients) of total patients. Among pediatric patients, the largest proportion of use was for patients aged 5-17 years, accounting for

approximately 83% (30 patients). Patients aged 0-4 years accounted for 17% (6 patients) of pediatric patients.

Table 2.2.1

Total number of patients with a prescription claim* for capecitabine from a study sample[†], stratified by patient age[‡], September 2011 through August 2015, aggregated

	September 2011 - August 2015	
	Patients N	Share %
Total Patients	104,037	100.0%
0-17 years	36	0.03%
0-4 years	6	16.7%
5-17 years	30	83.3%
18 years and older	103,998	99.96%
Unspecified age	3	0.003%

*Claims are from U S. commercial, Medicare Part D, Cash, and Medicaid plans.

[†]Study sample represents 17,614 outpatient pharmacies.

[‡]Age is at first claim during examined time period. Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-17 years include patients less than 18 years of age (17 years and 11 months).

Source: Symphony Health Solutions' Integrated Dataverse (IDV)TM. September 2011- August 2015. Extracted November 2015. File: SHSCPA 2015-1914 Xeloda, 11-17-2015

2.2.2 Prescriber Specialty

Table 2.2.2 provides the total number of patients with a prescription claim for capecitabine stratified by the top prescriber specialties, from September 2011 through August 2015, aggregated. During the examined period, approximately 80% (83,613 patients) of total patients with a prescription claim for capecitabine were from Oncology specialists. Internal Medicine and Hematology followed, accounting for 6.9% (7,196 patients) and 6.9% (7,172 patients), respectively. Pediatric specialists accounted for less than 0.5% (154 patients) of the total number of patients with a prescription claim for capecitabine (data not shown).³

Table 2.2.2

Total number of patients with a prescription claim* for capecitabine from a study sample[†], stratified by top prescriber specialties, September 2011 through August 2015, aggregated

	September 2011 - August 2015	
	Patients N	Share %
Total Patients	104,037	100.0%
Oncology	83,613	80.4%
Internal Medicine	7,196	6.9%
Hematology	7,172	6.9%
General Practice/Family Medicine	5,504	5.3%
All Other Specialties	7,056	6.8%

*Claims are from U.S. commercial, Medicare Part D, Cash, and Medicaid plans.

[†]Study sample represents 17,614 outpatient pharmacies.

Source: Symphony Health Solutions' Integrated Dataverse (IDV)[™], September 2011- August 2015. Extracted November 2015. File: SHSCPA 2015-1914 Xeloda, 11-17-2015

2.2.3 Diagnoses Data

An analysis of the total number of patients with a prescription claim for capecitabine AND a claim for the selected diagnosis codes of interest from September 2011 through August 2015 was also conducted. A total of 79,872 patients were captured with both a prescription claim for capecitabine AND a claim for a selected diagnosis from the study sample during the defined time period (data not shown).³ Among the 79,872 total patients with one or more of the diagnoses codes of interest, the adult population aged 18 years and older accounted for the vast majority of patients with approximately 99.9% (79,862 patients) of total patients compared to the pediatric population aged 0-17 years with less than 0.5% (7 patients) of total patients.

Due to the small sample size of pediatric patients with a pharmacy prescription claim for capecitabine AND a claim for the selected diagnosis codes of interest during the defined time period, further data analysis by diagnoses was not feasible.

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	September 14, 2015
Time Period of Search	April 30, 1998* - August 31, 2015
Search Type	Product Manufacturing Reporting Summary
Product Name(s)	Capecitabine (Product active ingredient)
Search Parameters	All ages, all outcomes, worldwide

* US Approval date

3.2 RESULTS

3.2.1 Total Number of FAERS Cases by Age

Table 3.2.1 Total Adult and pediatric FAERS cases* from April 30, 1998 to August 31, 2015 with capecitabine

	All reports (US)	Serious [†] (US)	Death (US)
Adults (≥ 18 years [€])	28,518 (11,891)	27,391 (10,865)	10,006 (4,977)
Pediatrics (0 - <18 years)	24 (16)	23 [‡] (15)	5 (3)

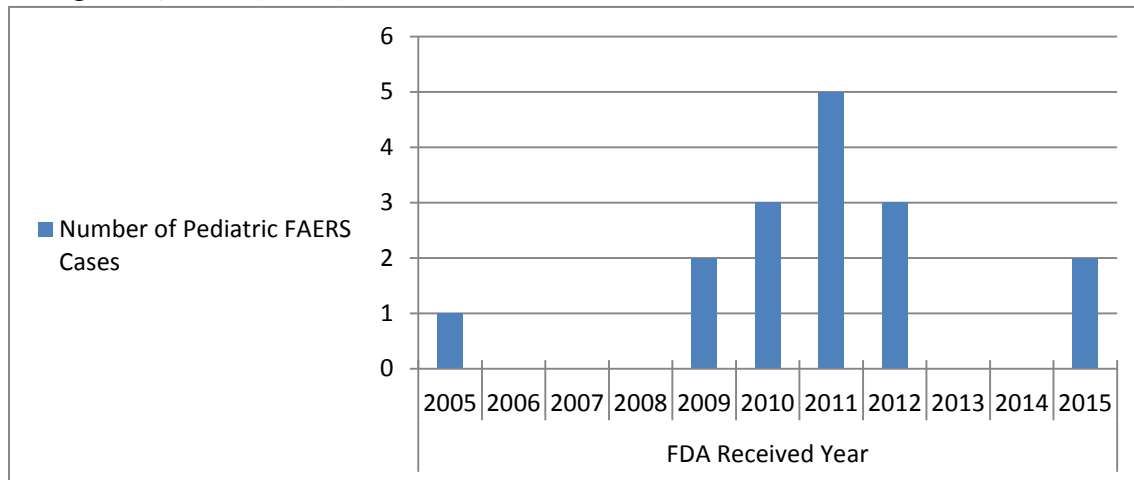
* May include duplicates and transplacental exposures, and have not been assessed for causality

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

€ The age range in this review was modified from ≥17 years to ≥18 years at the request of the Office of Pediatric Therapeutics staff at the capecitabine planning meeting on October 7, 2015.

‡ See Figure 3.2.2

Figure 3.2.1 Serious Pediatric Reports for capecitabine, by year of initial FDA receipt [April 30, 1998 to August 31, 2015] (n=16*)

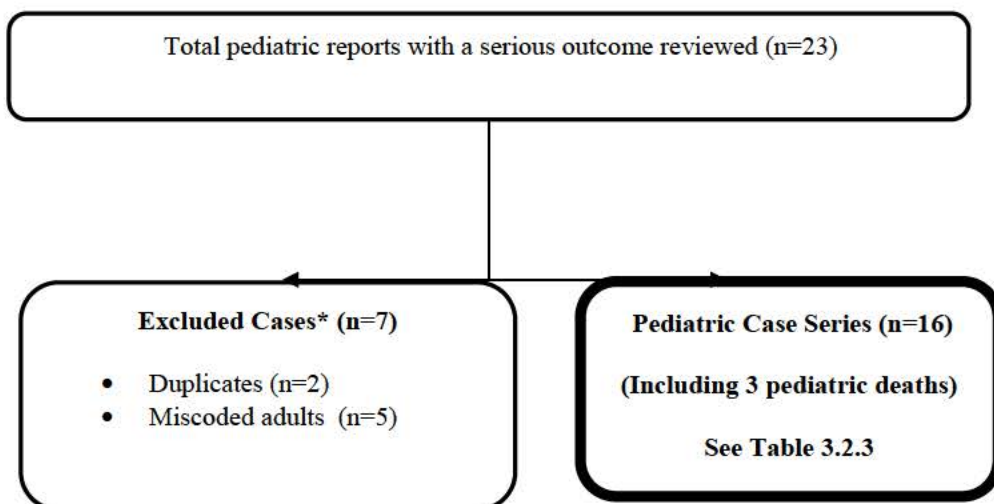


* Table 3.2.1 indicates 23 serious reports but after de-duplication and removal of miscoded adult patients, 16 serious pediatric reports remain in Figure 3.2.1

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified sixteen pediatric reports with a serious outcome after de-duplication and accounting for miscoded adult reports (See 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 Capecitabine



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

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.

Age (n=16)	0 - < 1 month	3
	1 month - <2 years	1
	2- < 6 years	2
	6- <12 years	6
	12- ≤ 18 years	4
Sex	Male	9
	Female	7
Country	United States	12
	Foreign	4
Reported Indication*	Glioma	10
	Colon Cancer	2
	Fetal exposure	3
	Accidental exposure	1
Serious Outcome [†]	Death	3
	Life-threatening	2
	Hospitalized	7
	Disability	5
	Congenital anomaly	2
	Other serious	8

-
- * Reported indication- the information that was provided in the indication field of the Medwatch report.
 - † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.
-

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=3)

Three cases reported death as an outcome. Two of the patients received multiple prior chemotherapy regimens and died due to disease progression after capecitabine initiation. The third patient died due to surgical complications related to *Clostridium difficile* infection.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=13)

There were three cases of fetal exposure to capecitabine, two of which reported ear malformations at birth and the third baby was born at 30 weeks with anemia which resolved.

There was one case of accidental exposure to capecitabine in a 22-month-old who ingested 3000mg with no adverse events reported.

The remaining nine cases are described below:

Labeled Events: Hand and foot syndrome, Dehydration and Renal Failure

An 11-year-old female enrolled in a study of Xeloda[®] plus radiation therapy in pediatric patients with newly diagnosed non-disseminated, intrinsic brainstem gliomas and high grade gliomas, developed grade 2 increased serum creatinine due to poor fluid intake after one week of capecitabine and grade 2 hand and foot syndrome five weeks after capecitabine initiation.

Reviewer's Comment: The events reported in this case are consistent with the known risks in the labeling and no increased severity was observed in this report.

Labeled Events: Irritability, Dysarthria

An 11-year-old male enrolled in an open-label, phase II study evaluating the safety and efficacy of the addition of capecitabine to radiation therapy compared to historical control in children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas developed irritability and slurred speech after three months of capecitabine/radiation. An MRI scan showed increase in tumor size and the adverse events were attributed to disease progression.

Labeled Event: Dysphagia

A 15-year-old male enrolled in an open-label, phase II study evaluating the safety and efficacy of the addition of capecitabine to radiation therapy compared to historical control in children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas developed dysphagia nine days after capecitabine/radiation therapy which resolved with ondansetron and lorazepam.

Unlabeled Event: CNS necrosis (n=4)

There were four cases of CNS necrosis at the tumor site from the open label, phase II study evaluating the safety and efficacy of the addition of capecitabine to radiation therapy compared to historical control in children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas. These patients were ages 4-15 years old and had received capecitabine/radiation therapy for 3-5 months prior to developing CNS necrosis on imaging. All patients received steroid treatment.

One of the CNS necrosis cases reported a 9-year-old female who also experienced the labeled event dyspnea due to aspiration pneumonia four months after starting capecitabine/radiation therapy. The dyspnea and pneumonia resolved with antibiotic treatment.

Reviewer's Comment: Baseline disease, disease progression, radiotherapy, and cytotoxic drug treatment are all contributing risk factors for CNS necrosis in glioma patients, and assigning causality to drug alone is not possible.

Unlabeled Event: Intracranial hemorrhage

A 4-year-old female enrolled in an open label, phase II study evaluating the safety and efficacy of the addition of capecitabine to radiation therapy compared to historical control in children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas, experienced a brainstem tumor-related hemorrhage after two months of capecitabine/radiation. At the time of the report, capecitabine treatment was ongoing.

Reviewer's Comment: Pre-existing/underlying disease, radiotherapy, and cytotoxic drug treatment area all contributing risk factors for intratumoral hemorrhage in glioma patients, and assigning causality to drug alone is not possible.

Unlabeled Event: Amnesia. Labeled Event: Dehydration

A 15-year-old female experienced short-term memory loss within 24 hours of receiving capecitabine and oxaliplatin for colon cancer. That same day, she also experienced dehydration. The reporter speculated the patient had “chemo brain/fog” but the outcome of the event was not reported.

Reviewer's Comment: Lack of information on the duration and outcome of amnesia (i.e. if it improved when hydration status was restored) limits causality assessment.

4 DISCUSSION

Drug utilization patterns for capecitabine were examined in order to assess its pediatric use and to provide context for the adverse event reports submitted to the FAERS database. The drug utilization analysis based on healthcare claims data from a study sample of outpatient pharmacies showed that the pediatric population aged 0-17 years accounted for less than 0.5% (36 patients) of total patients with a prescription claim for capecitabine from September 2011 through August 2015. Among pediatric patients, the largest proportion of use was for patients aged 5-17 years (30 out of 36 patients). Oncology specialists were the top prescribing specialty for capecitabine and pediatric specialists accounted for less than 0.5% of total patients. Due to the small sample size of pediatric patients with a pharmacy prescription claim for capecitabine AND a claim for a

selected diagnosis codes of interest during the defined time period, further data analysis by diagnoses was not feasible.

Our drug utilization analyses of capecitabine focused only on prescription claims from a sample of 17,614 outpatient pharmacies. Consequently, these patterns may not apply to other settings of care such as inpatient or other non-retail settings in which capecitabine may be used. Of note, the utilization data provided in this review are not nationally projected, as nationwide projections by age for capecitabine were not available at the time of the review. Therefore, it is unknown whether these data are representative of capecitabine use in the entire United States.

Of the sixteen pediatric reports reviewed, there were no new safety signals identified and no increased severity or frequency of any labeled adverse events. There were three deaths reported, however they can be attributed to disease-related and surgical complications.

5 CONCLUSION

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

6 RECOMMENDATIONS

Return to routine pharmacovigilance monitoring.

7 REFERENCES

1. Xeloda [package insert]. South San Francisco, CA: Genentech USA, Inc.; revised March 19, 2015.
2. IMS Health, IMS National Sales Perspectives™ Database. September 2011- August 2015. Extracted November 2015. File: NSP 2015-1914 Xeloda by Sup Ch, 11-17-2015.
3. Symphony Health Solutions' Integrated Dataverse (IDV)™. September 2011- August 2015. Extracted November 2015. File: SHSCPA 2015-1914 Xeloda, 11-17-2015.

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 from September 2011 through August 2015, capecitabine was primarily distributed to U.S. mail-order/specialty 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.

Symphony Health Solutions' Integrated Dataverse (IDV)™

The Symphony Health Solutions' Integrated Dataverse (IDV) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Data from Symphony Health Solutions' IDV provides patient counts with a pharmacy prescription claim for capecitabine from a sample of approximately 17,614 outpatient pharmacies. The universes of pharmacies contributing to these data are unknown; therefore, nationwide projections are not available at this time, and it is unknown whether these data are representative of capecitabine use in the entire U.S.

Although the claims data analysis is suggestive of off-label use of capecitabine in the pediatric population for the selected diagnoses groups of cancer, many limitations prohibit the use of claims based analyses solely to determine the prevalence or extent of off-label use. First, diagnosis codes used in claims data analysis are generated for billing purposes - not for clinical care or research- and thus may reflect billing practices and not true disease prevalence. Second, the medical claims data used in our analyses were not validated by medical records to make sure that the coded diagnoses are truly reflective of the patients' clinical conditions. Therefore, the estimates provided may be overestimates of the true number because provisional or rule-out diagnoses may have been included. Third, there is also no direct linkage in the claims data

between drug and diagnosis, meaning that we cannot assume that these diagnoses represent actual indications for the drug treatment. Finally, it is also important to note that diagnoses were captured if a claim with the selected ICD-9 diagnoses codes was made within 180 days prior to or 180 days subsequent to any capecitabine claim. The exact time correlation between when diagnosis claims were billed in relation to capecitabine claims was not examined in this study. Therefore, any diagnosis claims billed outside the observed time periods were not captured.

8.2 APPENDIX B. DRUG UTILIZATION STUDY PARAMETERS

Drug Name	National Drug Codes (NDCs)
CAPECITABINE	00093747306
CAPECITABINE	00093747489
CAPECITABINE	00378251191
CAPECITABINE	00378251278
CAPECITABINE	16729007212
CAPECITABINE	16729007329
CAPECITABINE	42291019060
CAPECITABINE	42291019112
CAPECITABINE	51079051005
XELODA	00004110020
XELODA	00004110051
XELODA	00004110116
XELODA	00004110150
XELODA	00004110175
XELODA	54569571700
XELODA	54868414300
XELODA	54868414301
XELODA	54868414302
XELODA	54868526000
XELODA	54868526001
XELODA	54868526002
XELODA	54868526003
XELODA	54868526004
XELODA	54868526005
XELODA	54868526006
XELODA	54868526007
XELODA	54868526008
XELODA	54868526009
XELODA	68258903601

Diagnosis Group	ICD-9 Diagnoses Codes
Colon Cancer	153 MALIGNANT NEOPLASM OF COLON 153 0 MAL NEO HEPATIC FLEXURE 153 1 MAL NEO TRANSVERSE COLON 153 2 MAL NEO DESCEND COLON 153 3 MAL NEO SIGMOID COLON 153 4 MALIGNANT NEOPLASM CECUM 153 5 MALIGNANT NEO APPENDIX 153 6 MALIG NEO ASCEND COLON 153 7 MAL NEO SPLENIC FLEXURE 153 8 MALIGNANT NEO COLON NEC 153 9 MALIGNANT NEO COLON NOS 197 5 SEC MALIG NEO LG BOWEL 230 3 CA IN SITU COLON
Colorectal Cancer	153 MALIGNANT NEOPLASM OF COLON 153 0 MAL NEO HEPATIC FLEXURE 153 1 MAL NEO TRANSVERSE COLON 153 2 MAL NEO DESCEND COLON 153 3 MAL NEO SIGMOID COLON 153 4 MALIGNANT NEOPLASM CECUM 153 5 MALIGNANT NEO APPENDIX 153 6 MALIG NEO ASCEND COLON 153 7 MAL NEO SPLENIC FLEXURE 153 8 MALIGNANT NEO COLON NEC 153 9 MALIGNANT NEO COLON NOS 197 5 SEC MALIG NEO LG BOWEL 230 3 CA IN SITU COLON 154 MAL NEO RECTUM/RECTOSIG/ANUS 154 0 MAL NEO RECTOSIGMOID JCT 154 1 MALIGNANT NEOPL RECTUM 154 2 MALIG NEOPL ANAL CANAL 154 3 MALIGNANT NEO ANUS NOS 154 8 MAL NEO RECTUM/ANUS NEC 230 4 CA IN SITU RECTUM 230 5 CA IN SITU ANAL CANAL 230 6 CA IN SITU ANUS NOS
Breast Cancer	174 MALIGNANT NEO FEMALE BREAST 174 0 MALIG NEO NIPPLE 174 1 MAL NEO BREAST-CENTRAL 174 2 MAL NEO BREAST UP-INNER 174 3 MAL NEO BREAST LOW-INNER 174 4 MAL NEO BREAST UP-OUTER 174 5 MAL NEO BREAST LOW-OUTER 174 6 MAL NEO BREAST-AXILLARY 174 8 MALIGN NEOPL BREAST NEC 174 9 MALIGN NEOPL BREAST NOS 175 MALIGNANT NEO MALE BREAST 175 0 MAL NEO MALE NIPPLE 175 9 MAL NEO MALE BREAST NEC 198 81 SECOND MALIG NEO BREAST 233 CA IN SITU BREAST 233 0 CA IN SITU BREAST

Diagnosis Group	ICD-9 Diagnoses Codes
Brain Cancer <i>(unapproved indications)</i>	191 MALIGNANT NEOPLASM OF BRAIN 191 0 MALIGN NEOPL CEREBRUM 191 1 MALIG NEO FRONTAL LOBE 191 2 MAL NEO TEMPORAL LOBE 191 3 MAL NEO PARIETAL LOBE 191 4 MAL NEO OCCIPITAL LOBE 191 5 MAL NEO CEREB VENTRICLE 191 6 MAL NEO CEREBELLUM NOS 191 7 MAL NEO BRAIN STEM 191 8 MALIG NEO BRAIN NEC 191 9 MALIG NEO BRAIN NOS
Esophageal Cancer <i>(unapproved indications)</i>	150 MALIGNANT NEO ESOPHAGUS 150 0 MAL NEO CERVICAL ESOPHAG 150 1 MAL NEO THORACIC ESOPHAG 150 2 MAL NEO ABDOMINAL ESOPHAGUS 150 3 MAL NEO UPPER 3RD ESOPH 150 4 MAL NEO MIDDLE 3RD ESOPH 150 5 MAL NEO LOWER 3RD ESOPH 150 8 MAL NEO ESOPHAGUS NEC 150 9 MAL NEO ESOPHAGUS NOS 230 1 CA IN SITU ESOPHAGUS
Gastric Cancer <i>(unapproved indications)</i>	151 MALIGNANT NEO STOMACH 151 0 MAL NEO STOMACH CARDIA 151 1 MALIGNANT NEO PYLORUS 151 2 MAL NEO PYLORIC ANTRUM 151 3 MAL NEO STOMACH FUNDUS 151 4 MAL NEO STOMACH BODY 151 5 MAL NEO STOM LESSER CURV 151 6 MAL NEO STOM GREAT CURV 151 8 MALIG NEOPL STOMACH NEC 151 9 MALIG NEOPL STOMACH NOS 230 2 CA IN SITU STOMACH
Pancreatic Cancer <i>(unapproved indications)</i>	157 MALIGNANT NEOPLASM PANCREAS 157 0 MAL NEO PANCREAS HEAD 157 1 MAL NEO PANCREAS BODY 157 2 MAL NEO PANCREAS TAIL 157 3 MAL NEO PANCREATIC DUCT 157 4 MAL NEO ISLET LANGERHANS 157 8 MALIG NEO PANCREAS NEC 157 9 MALIG NEO PANCREAS NOS

8.3 APPENDIX C. 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.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=16)

Case Number	Version Number	Manufacturer Control Number
10452076	7	BR-ROCHE-1460294
11159088	1	FR-BAXTER-2015BAX028510
5815613	1	FR-ROCHE-406322
6905015	3	US-ROCHE-611935
7054688	1	US-ROCHE-636130
7145115	1	US-ROCHE-659795
7364351	6	US-ROCHE-692702
7441235	1	US-ROCHE-711176
7691269	3	US-ROCHE-744418
7843943	3	US-ROCHE-762330
7948152	5	US-ROCHE-775742
7998021	1	US-ROCHE-781471
8052453	1	US-ROCHE-789747
8339229	1	US-ROCHE-1030275
8397823	2	US-ROCHE-1033709
8887981	1	DSA_60404_2012

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

/s/

MARGARET L RAND
02/23/2016

KUSUM S MISTRY
02/23/2016

The drug use data in this review has been cleared by the database vendors.

MOHAMED A MOHAMOUD
02/23/2016

SHAILY ARORA
02/23/2016

GRACE CHAI
02/23/2016

STEVEN C JONES
02/23/2016