Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	August 2, 2016	
Safety Evaluator:	Timothy Jancel, PharmD, BCPS-AQ ID Division of Pharmacovigilance II (DPV II)	
Drug Use Analyst:	Nabila Sadiq, PharmD Division of Epidemiology (DEPI II)	
Team Leaders:	Kelly Cao, PharmD Division of Pharmacovigilance II (DPV II) Justin Mathew, PharmD Division of Epidemiology (DEPI II)	
Deputy Division Director:	LCDR Grace Chai, PharmD Deputy Director for Drug Utilization Division of Epidemiology II (DEPI II)	
Division Director (acting):	S. Christopher Jones, PharmD, MS, MPH Division of Pharmacovigilance II (DPV II)	
Product Name:	Entecavir (Baraclude®)	
Pediatric Labeling Approval Date:	March 20, 2014	
Application Type/Number:	NDA	021797 Oral tablet, 0.5 mg and 1 mg
	NDA	021798 Oral solution, 0.05 mg/mL
	ANDA	202122 Oral tablet, 0.5 mg and 1 mg
	ANDA	205740 Oral tablet, 0.5 mg and 1 mg
	ANDA	206217 Oral tablet, 0.5 mg and 1 mg
	ANDA	206652 Oral tablet, 0.5 mg and 1 mg
Applicant/Sponsor:	NDAs	Bristol Myers Squibb
	ANDAs	Teva Pharmaceuticals
		Hetero Labs
		Aurobindo Pharmaceutical
		Amneal Pharmaceuticals
OSE RCM #:	2016-348	

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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 Baraclude® (entecavir) in pediatric patients.

Entecavir is an oral guanosine nucleoside analog that inhibits hepatitis B virus (HBV) polymerase. It was initially approved in March 2005 for the treatment of chronic HBV infection in adults and adolescents 16 years of age and older.

In March 2014, a product labeling revision was approved which expanded the patient population to include pediatric patients 2 years of age and older with chronic HBV infection with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease.

From March 2014 through February 2016, a nationally estimated number of 37,825 patients received a dispensed prescription for entecavir from U.S. outpatient retail pharmacies, of which the pediatric population aged 0-16 years, accounted for less than 1% of the total patients. Of the pediatric patients, entecavir use was only identified in patients aged 2-16 years.

The Food and Drug Administration Adverse Event Reporting System (FAERS) database was searched for all adverse event reports from March 29, 2005 through February 29, 2016. The FAERS review focused on the serious pediatric reports identified in this time period. A case series was established by the identification of all pediatric cases with fatal outcomes (n=0) or those with serious, unlabeled adverse events (n=4). Limitations to the four serious, unlabeled adverse event cases include incomplete case descriptions, underlying disease processes, concurrent disease states or medications, or other coincidental factors. There is no evidence from these data that there are new pediatric safety concerns with entecavir at this time. The Division of Pharmacovigilance (DPV) will continue routine post marketing surveillance of all adverse events associated with the use of entecavir in pediatric patients.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY[1,2]

Entecavir (Baraclude®) tablets and oral solution were initially approved on March 28, 2005 for the treatment of chronic hepatitis B virus (HBV) infection in patients 16 years of age and older.

Table 1.1.1 describes the recommended dosage in adult patients.

Table 1.1.1 Recommended Entecavir Dosage in Adult Patients	
Compensated Liver Disease	• The recommended dose of entecavir for chronic HBV infection in nucleoside-inhibitor-treatment-naïve adults and adolescents 16 years of age and older is **0.5 mg once daily** • The recommended dose of entecavir in adults and adolescents (at least 16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine or telbivudine resistance substitutions rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L is **1 mg once daily**
Decompensated Liver Disease	• The recommended dose of entecavir for chronic HBV infection in adults with decompensated liver disease is **1 mg once daily**

The pharmacokinetics, safety, and antiviral activity of entecavir in pediatric patients were initially assessed in study AI463028. Subsequently, safety and antiviral efficacy were confirmed in study AI463189. The adverse reactions observed in pediatric patients who received treatment with entecavir in both of these studies were consistent with those observed in clinical trials of entecavir in adults. Adverse drug reactions reported in greater than 1% of pediatric subjects included abdominal pain, rash events, poor palatability, nausea, diarrhea, and vomiting.[1,2]

Study AI463028

A Phase 2b, multinational, single arm, open-label study to assess the pharmacokinetics, safety, tolerability and preliminary efficacy of entecavir in pediatrics subjects with chronic HBV infection aged 2 to 18 years. Twenty-four treatment-naïve and 19 lamivudine-experienced HBeAg-positive pediatric subjects 2 to less than 18 years of age with compensated chronic HBV infection and elevated alanine aminotransferase (ALT) were treated with entecavir 0.015 mg/kg (up to 0.5 mg) or 0.03 mg/kg (up to 1 mg) once daily. Fifty-eight percent (14/24) of treatment-naïve subjects and 47% (9/19) of lamivudine-experienced subjects achieved HBV DNA <50 IU/mL at Week 48 and ALT normalized in 83% (20/24) of treatment-naïve and 95% (18/19) of lamivudine-experienced subjects. Study AI463028 confirmed the doses selected in both patient populations and provided the basis for initiating study AI463189.

Study AI463189

A Phase 3, multinational, randomized, double-blind, placebo controlled study to assess the efficacy and safety of entecavir in pediatric patients with chronic HBV infection who were HBeAg positive and nucleoside-inhibitor-treatment-naïve pediatric patients 2 to less than 18 years of age. The primary efficacy endpoint was a composite of HBeAg seroconversion and serum HBV DNA <50 IU/mL at week 48 assessed in the first 123 patients reaching 48 weeks of blinded treatment. Twenty-four percent (20/82) of patients in the entecavir-treated group and 2% (1/41) of patients in the placebo-treated group met the primary endpoint. Forty-six percent (38/82) of entecavir-treated patients and 2% (1/41) of placebo-treated patients achieved HBV DNA <50 IU/mL at week 48.

Table 1.1.2 describes the recommended dose of entecavir for pediatric patients 2 years of age or older and weighing at least 10 kg. The oral solution should be used for patients with body weight up to 30 kg.

Table 1.1.2. Recommended Entecavir Dosage in Pediatric Patients

	Recommended Once-Daily Dose of Oral Solution (mL)	
Body Weight (kg)	**Treatment-Naïve Patients[a]**	**Lamivudine-Experienced Patients[b]**
10 to 11	3	6
Greater than 11 to 14	4	8
Greater than 14 to 17	5	10
Greater than 17 to 20	6	12
Greater than 20 to 23	7	14
Greater than 23 to 26	8	16
Greater than 26 to 30	9	18
Greater than 30	10	20

[a] Children with body weight greater than 30 kg should receive 10 mL (0.5 mg) or oral solution or one 0.5 mg tablet once daily

[b] Children with body weight greater than 30 kg should receive 20 mL (1 mg) of oral solution or one 1 mg tablet once daily

DPV has not completed any further pediatric reviews for entecavir. To our knowledge, there is no pending regulatory action involving new safety information for this drug in the pediatric population.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES[2]

The Baraclude® (entecavir) label includes the following information:

CONTRAINDICATIONS

- None

WARNINGS AND PRECAUTIONS

- Severe acute exacerbations of hepatitis B virus infection after discontinuation: Monitor hepatic function closely for at least several months
- Co-infection with HIV: BARACLUDE is not recommended unless the patient is also receiving highly active antiretroviral therapy (HAART)
- Lactic acidosis and severe hepatomegaly with steatosis: If suspected, treatment should be suspended

ADVERSE REACTIONS

- Most common adverse reactions (≥3%, all severity grades) are headache, fatigue, dizziness, and nausea

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue nursing or BARACLUDE taking into consideration the importance of BARACLUDE to the mother
- Liver transplant recipients: Limited data on safety and efficacy are available

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 entecavir is distributed by the manufacturer. Sales distribution data for 2015 showed that approximately 55% of entecavir bottles were sold to U.S. outpatient retail pharmacies, followed by 12% to non-retail settings (mostly long-term care and clinics) and 33% 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 prescription for entecavir from U.S. outpatient retail pharmacies, stratified by patient age groups 0-1, 2-16 and 17+ years and older from March 1, 2014 through February 29, 2016, cumulative.

2.2 RESULTS

Table 2
Nationally estimated number of patients who received a dispensed prescription for entecavir, stratified by patients age, from U.S. Outpatient retail pharmacies, March 2014 - February 2016

	March 1, 2014- February 29, 2016	
	Patients (N)	**Share (%)**
Entecavir Total Patients	**37,825**	**100.00%**
0-16 (age in years)	**144**	**0.38%**
0-1 years	--	--
2-16 years	144	0.38%
17+ years and older	**37,660**	**99.56%**
Unknown age	**279**	**0.74%**

*Unique patient counts 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 the individual categories.
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include <17 years of age (16 years and 11 months).
Source: IMS, Vector One®: Total Patient Tracker. March 2014 - February 2016. Extracted March-2016. File 2016-348-TPT-Entecavir-BPCA-Custom Age Group Report. March 2014- February 2016. 03.31.2016.xlsx

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	March 3, 2016
Time Period of Search	March 29, 2005* - February 29, 2016
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Names	Baraclude, Entecavir
Search Parameters	All ages, all outcomes, worldwide

** Initial US Approval Date*

3.1.2 Inclusion Criteria for Pediatric Case Series

All FAERS reports retrieved were analyzed and reviewed. For the purposes of this review, DPV included pediatric cases that reported:

- Fatal outcomes, OR
- Serious, unlabeled adverse events

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 29, 2005 through February 29, 2016 with Entecavir

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	1829 (558)	1581 (323)	431 (109)
Pediatrics (0 - <17 years)	32 (10)	**27‡ (6)**	1 (0)

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

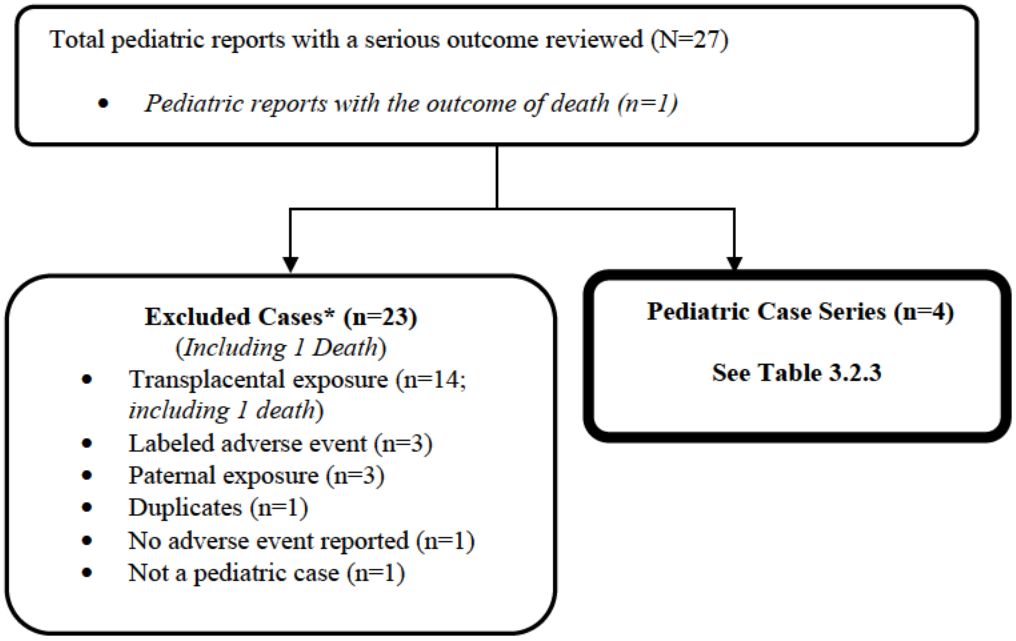
† For the purposes of this review, the following outcomes qualify as serious: ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

‡ See Figure 3.2.2

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 27 pediatric reports with a serious outcome (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 Entecavir



* 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.

Table 3.2.3 Characteristics of Pediatric Case Series with Entecavir (N=4)

Age	2 - < 6 years	1
	6 - <12 years	1
	12 - < 17 years	2
Sex	Male	2
	Female	1
	Unknown	1
Country	United States	2
	Foreign	2
Reported Reason for Use	HBV infection	3
	Unknown	1
Serious Outcome*	Hospitalized	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.

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

No pediatric deaths were identified in this review.

3.4 SUMMARY OF SERIOUS, NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=4)

FAERS# 8064524
Country: Korea
Initial FDA Received Date: August 2, 2011
A 15-year-old patient was hospitalized due to deterioration of the liver after administration of entecavir. Entecavir indication, dose, route, frequency, and duration were not reported. No other clinical details or laboratory values were reported.
Reviewer Comments: *Limited case details precluded a meaningful causality assessment.*

FAERS# 9050401
Country: USA
Initial FDA Received Date: February 5, 2013
A 9-year-old male received oral entecavir solution (0.33 mg daily) for chronic HBV. Due to increased weight, the daily dose was increased to 0.5 mg once daily. He experienced what was described as a good response with a dramatic drop in HBV DNA count and normalization of liver enzymes. He started entecavir in the spring, but by the summer of the following year, he developed precocious puberty. He was seen by an endocrinologist in the fall, and was noted to be at Tanner Stage II. Concomitant medications included lisdexamfetamine, polyethylene glycol, sertraline, ranitidine, and risperidone. Medical conditions included fetal alcohol syndrome, deafness secondary to congenital syphilis, prematurity, failure to thrive, food refusal, dysfunctional swallowing, developmental delay, constipation, attention deficit-hyperactivity disorder, autism spectrum disorder, and dysmorphic disorder. His prior treatment for HBV included monotherapy with interferon for four months in 2006. It was also noted that his medications were not discontinued in response to the event. Outcome of the event was considered to be ongoing.
Reviewer Comments: *The reported adverse event of precocious puberty is confounded by the concomitant administration of risperidone. Risperidone is labeled for precocious puberty under Postmarketing Experience.*[3]

FAERS# 10015903
Country: Lebanon
Initial FDA Received Date: March 17, 2014
A 12-year-old male received oral entecavir (0.25 mg daily). For the first six months of HBV treatment, he received peginterferon alfa-2a (Pegasys®) with entecavir. After approximately three and one-half years on entecavir, it was reported he had poor concentration in school and a neurologist confirmed seizure. He did not require hospitalization and he received phenobarbital and carbamazepine. He was not receiving interferon at the time of the neurologic adverse event. Past medical history, outcome, and the reporter's causality assessment were not reported.
Reviewer Comments: *Limited case details precluded a meaningful causality assessment.*

FAERS# 10332012
Country: USA
Initial FDA Received Date: July 22, 2014
A 5-year-old female received oral entecavir solution (0.225 mg daily) during a clinical study of chronic HBV. The purpose of the study was to determine the safety and efficacy of treatment using a combination of drugs (entecavir and pegylated interferon) in children with immunotolerant chronic HBV. Around the eighth week of entecavir therapy (interferon had not started yet), she received routine immunizations of varicella-zoster, hepatitis A, diphtheria, tetanus, and pertussis. The following day, she passed out at school, developed a seizure, and was taken to the emergency room where an x-ray revealed pneumonia. The final diagnosis was reported as seizure secondary to fever which might be related to either vaccination or pneumonia. The reporter was not sure if fever was related to vaccination or pneumonia. Past medical history was significant for cleft palate repair. The reporter's causality assessment stated febrile seizure and pneumonia were not related to entecavir therapy; febrile seizure was possibly related to varicella-zoster vaccine, hepatitis A virus vaccine, and diphtheria, tetanus and pertussis vaccine.
Reviewer Comments: *The reported events were confounded by multiple vaccinations the day prior to the seizure event, underlying pneumonia, and fever. Some vaccines are labeled for seizure; however, febrile seizures are relatively rare after vaccination.*

4 DISCUSSION

Analysis of drug utilization data shows pediatric patients accounted for less than 1% of the total patients who received a dispensed prescription for entecavir from outpatient retail pharmacies. Among the pediatric patients, entecavir use was only identified in pediatric patients aged 2-16 years; no entecavir use was seen for patients aged 0-1 year. DPV identified FAERS reports across all pediatric age groups, patients aged 2 years and older. Of note, we focused the drug utilization analyses on the outpatient retail pharmacy setting only where the largest proportion of entecavir sales was distributed. However, it is important to note that these estimates may not be representative of all treatment for HBV in the U.S. and should be interpreted with caution.

We focused our FAERS analysis on the pediatric cases with unlabeled adverse events and serious outcomes associated with entecavir use. Four cases were identified for inclusion in the case series. No new safety signals were identified. Limitations to case interpretation included incomplete case descriptions, underlying disease processes, concurrent disease states or medications, or other coincidental factors. DPV will continue routine postmarketing surveillance for entecavir.

5 CONCLUSION

Overall, there were no patterns or trends in drug utilization or in the FAERS cases series to suggest a new safety signal was associated with entecavir. The reported adverse events in the four serious, unlabeled cases may be due to underlying disease processes, concurrent disease states or medications, or other coincidental factors.

6 RECOMMENDATIONS

DPV does not recommend any labeling changes at this time. DPV will continue routine monitoring of the adverse event reports associated with the use of entecavir.

7 REFERENCES

1. Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937.htm. Accessed: May 2016.
2. Baraclude® (entecavir), NDAs 021797, 021798 - Approved Product Label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021797s018,021798s019lbl.pdf. Accessed: May 2016.
3. Risperdal® (risperidone), NDA 020272 – Approved Product Label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020272s077,020588s065,021346s055,021444s051lbl.pdf. Accessed: May 2016.

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, entecavir 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.

The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

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 ENTECAVIR (N=4)

FAERS Case Number	FAERS Version Number	Manufacturer Control Number
8064524	1	KR-BRISTOL-MYERS SQUIBB COMPANY-15930555
9050401	1	US-BRISTOL-MYERS SQUIBB COMPANY-17324328
10015903	2	LB-BRISTOL-MYERS SQUIBB COMPANY-20364790
10332012	3	US-BRISTOL-MYERS SQUIBB COMPANY-20752374

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TIMOTHY J JANCEL
08/02/2016

NABILA SADIQ
08/02/2016
Vendor Clearance done on 06/30/2016

JUSTIN A MATHEW
08/02/2016

KELLY Y CAO
08/02/2016

GRACE CHAI
08/03/2016

STEVEN C JONES
08/03/2016