FDA Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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Cover page Case ID(s) with an asterisk ('*') indicate an invalid status and are not captured in the body of the report.

Esub Case ID(s) Submitted:

8915704	**9452383**	**11105081**	**11225746**	**11275144**	**12103690**	**13264782**
14567908	**14686667**	**14882044**	**14882047**	**14882048**	**14882049**	

Run by: CREWP

Date - Time: 21-SEP-2018 14:23 PM

Total number of cases (Esub): 13

Total number of inactive cases: 0

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 8915704

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** DEU **Event Date:** 10-Aug-2010 **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 09-Aug-2018 **Mfr Rcvd Date:** 31-Jul-2018 **Mfr Control #:** DE-009507513-1009DEU00132B1 **Application #:** 022145

Patient Information:

Age: < 1 DAY **Sex:** Male **Weight:** 1.6 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ISENTRESS			Transplacental	UNK	HIV infection		
2	NORVIR			Transplacental	UNK	HIV infection		
3	PREZISTA			Transplacental	UNK	HIV infection		
4	TRIZIVIR			Transplacental	UNK	HIV infection		
5	VIREAD			Transplacental	UNK	HIV infection		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ISENTRESS		NA	NA				MERCK	
2	NORVIR		NA	NA					
3	PREZISTA		NA	NA					
4	TRIZIVIR		NA	NA					
5	VIREAD		NA	NA					

Event Information:

Preferred Term (MedDRA Â© Version: 21.0)	ReC
Foetal exposure during pregnancy	NA
Hemivertebra	NA

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Maternal drugs affecting foetus	NA
Oesophageal atresia	NA
Premature baby	NA
Small for dates baby	NA
Spine malformation	NA

Event/Problem Narrative:

Information has been received for the Antiretroviral Pregnancy Registry (from a physician) concerning a male patient (APR numbers: ID (b) (6), Baby ID (b) (6), Mother ID # (b) (6) and (b) (6)). The patient's mother history included one pregnancy/life birth without congenital anomaly (date not reported). On 29-NOV-2008, the patient's mother was placed on therapy with raltegravir potassium (ISENTRESS), 400 mg, twice a day for the treatment of HIV infection. Other suspect therapies included abacavir sulfate (+) lamivudine (+) zidovudine (TRIZIVIR), 300-150-300 mg, twice a day for the treatment of HIV infection (therapy started on 29-NOV-2008), tenofovir disoproxil fumarate (VIREAD), 245 mg, once a day for the treatment of HIV infection (therapy started on 29-NOV-2008, ritonavir (NORVIR), 100 mg, twice a day for the treatment of HIV infection (therapy started on 29-NOV-2008), and darunavir (PREZISTA), 600 mg, twice a day for the treatment of HIV infection (therapy started on 29-NOV-2008) and also unspecified antiretroviral therapies.

At the beginning of (b) (6), the patient's mother became pregnant (noticed at the end of the first trimester; LMP (b) (6), EDD (b) (6)) (WAES #1009DEU00132). At that time, the patient's clinical indicators were asymptomatic, acute (primary) HIV, CD4+ T-cell category greater/ equal to 500 microliters. Therapy with raltegravir potassium (ISENTRESS), abacavir sulfate (+) lamivudine (+) zidovudine (TRIZIVIR), tenofovir disoproxil fumarate (VIREAD), ritonavir (NORVIR) and darunavir (PREZISTA) continued. The course of pregnancy was not reported. No prenatal tests were done.

On (b) (6), inpatient cesarean section was performed (reason not reported) and the mother delivered a male, premature, small for dates baby (gestational age 33 weeks, birth weight 1,600 grams, length 44 cm, head circumference 33 cm) with congenital anomalies of esophageal atresia (IIIb), butterfly vertebra (T10) and hemivertebra (T9) (previously reported as "total occlusion of the esophagus, an additional rib (unilateral) and vertebral body deformation"). Operation of the esophageal atresia was performed. Subsequently, the baby was doing well, however, the outcome was not clearly stated.

Additional information received from the APR on 12-JAN-2011 provided the birth defect evaluator's assessment. The birth defect evaluator considered esophageal atresia (IIIb) is a failure of the esophagus to form completely so there is an interruption between the pharynx and the stomach, it is a primary malformation of the GI tract in the early first trimester, the development of this defect and the timing of the exposure to drug cannot rule out a possible association; butterfly vertebra (T10) is a primary abnormal formation of the vertebra(e) in which the bilateral asymmetry of the vertebra is disrupted, this is an early/mid first trimester defect, the development of this defect and the timing of the exposure to drug cannot rule out a possible association; hemivertebra (T9) is a primary abnormal formation of the vertebra(e) in which the bilateral

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asymmetry of the vertebra is disrupted, this is an early/mid first trimester defect, the development of this defect and the timing of the exposure to drug cannot rule out a possible association.

The reporting physician was unsure about the drug relationship concerning the development of esophageal atresia (IIIb), butterfly vertebra (T10) and hemivertebra (T9) and therapy with raltegravir potassium (ISENTRESS), abacavir sulfate (+) lamivudine (+) zidovudine (TRIZIVIR), tenofovir disoproxil fumarate (VIREAD), ritonavir (NORVIR) and darunavir (PREZISTA). The physician had previously stated that the treating pediatricians felt that the congenital anomalies of total occlusion of the esophagus, an additional rib (unilateral) and vertebral body deformation were rather not related to therapy with raltegravir potassium.

Follow-up information received on 20-OCT-2010 contained the following adverse experiences: premature baby ((b) (6)), small for dates baby (b) (6) .

Additional information was obtained on request by the Company from the FDA under the Freedom of Informaiton Act. This was reported through Johnson & Johnson (Company report # 20101000081). The original reporting source was not provided.

Additional information was obtained on request by the Company from the FDA under the Freedom of Informaiton Act. This was concerning a patient who on an unspecified date was placed on an unspecified antiretroviral and experience a maternal drug affecting foetus. At the time of the report, the patientÂs outcome was not provided.

Upon internal review, Oesophageal atresia, Hemivertebra, Spine malformation, Maternal drugs affecting foetus were determined to be medically significant.

The events Oesophageal atresia, Hemivertebra, Spine malformation were considered serious due to congenital anomaly.

The mothers experience has been captured in 1009DEU00132.

Follow-up information has been received for the Antiretroviral Pregnancy Registry from a healthcare professional on 14-JUN-2018. The patient's birth defects were reported as butterfly vertebra (T10) (Anomaly of thoracic vertebra/other musculoskeletal defects/D/2), esophageal atresia (IIIB) (esophageal atresia without tracheoesophageal fistula/Upper gastrointestinal system/D/2) and hemivertebra (T9) (Anomaly of thoracic vertebra/ other musculoskeletal defects/D/2)

It has been determined that case # 1209USA003673 is a duplicate of Case # 1009DEU00132B1 Therefore, case # 1209USA003673 is being deleted from our files and the cases consolidated into case # 1009DEU00132B1.

Follow-up information was received from the Antiretroviral Pregnancy Registry on 31-JUL-2018 confirming that the exposure to raltegravir potassium (ISENTRESS) occurred prior to conception.

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Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
HIV infection			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: MERCK

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 9452383

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 27-Dec-2013 **Mfr Rcvd Date:** 18-Dec-2013 **Mfr Control #:** US-JNJFOC-20130802277 **Application #:** 021976

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	PREZISTA			Transplacental		Product used for unknown indication		
2	ISENTRESS			Transplacental		Product used for unknown indication		
3	NORVIR			Transplacental		Product used for unknown indication		
4	TENOFOVIR			Transplacental		Product used for unknown indication		
5	TRIZIVIR			Transplacental		Product used for unknown indication		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	PREZISTA		NA	No					
2	ISENTRESS		NA	NA					
3	NORVIR		NA	NA					
4	TENOFOVIR		NA	NA					
5	TRIZIVIR		NA	NA					

Event Information:

Preferred Term (MedDRA © Version: 21.0)	ReC
Foetal exposure during pregnancy	NA
Hemivertebra	NA

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Oesophageal atresia	NA
Spine malformation	NA

Event/Problem Narrative:

This spontaneous report was received from a health professional, via the Canadian Health Authority and concerns a newborn baby of unspecified sex from The United States.

The patient's weight, height and relevant medical history were not reported. The patient's mother was treated with darunavir (tablets, unknown) dose and frequency unspecified, initiated on an unspecified date along with non-company suspect drugs: tenofovir (unspecified, unknown), abacavir with lamivudine/zidovudine (unspecified, unknown), raltegravir (unspecified, unknown) and ritonavir (unspecified, unknown) all drugs initiated on an unspecified date for an unspecified indication. The patient's mother was treated with the drugs while she was pregnant and the infant was exposed to these drugs via transplacental route characterized as drug exposure in utero. Concomitant medications were not reported. On an unspecified date, the patient experienced spine malformation, oesophageal atresia and hemivertebra. Action taken with darunavir, tenofovir, abacavir with lamivudine/zidovudine, raltegravir and ritonavir was not applicable. The patient had recovered from drug exposure in utero on an unspecified date and the outcome of spine malformation, oesophageal atresia and hemivertebra was not reported.

This report was serious (congenital anamoly, medically significant).

This parent/child case is linked to 20130802276.

Additional information was received on 18-DEC-2013.

The brand names of the suspects drug: PREZISTA (darunavir) and non-company suspect drugs: trizivir (abacavir with lamivudine/zidovudine), raltegravir ritonavir were updated. Other identification numbers (baby registry and health care professional) numbers were updated to the case.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?

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FOIA Case Report Information

Case ID: 9452383

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: JANSSEN

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 11105081

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** GBR **Event Date:** 14-Jun-2008 **Outcomes:** CA,DS,HO,LT,OT, **Application Type:** NDA

FDA Rcvd Date: 06-Sep-2018 **Mfr Rcvd Date:** 29-Aug-2018 **Mfr Control #:** GB-GILEAD-2015-0152641 **Application #:** 021752

Patient Information:

Age: < 1 DAY **Sex:** Female **Weight:** KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TRUVADA		1 DF/QD	Transplacental	1 DF, QD	HIV infection	(b) (6)	
2	APTIVUS			Transplacental	UNK, U			
3	APTIVUS		500 MG/BID	Transplacental	500 mg, bid	HIV infection		
4	APTIVUS		500 MG/QD	Transplacental	500 mg, QD			
5	ETRAVIRINE		400 MG/BID	Transplacental	400 mg, bid			
6	ETRAVIRINE		1000 MG/QD	Transplacental	1000 mg, qid	Product used for unknown indication		
7	INTELENCE			Transplacental	UNK, U			
8	INTELENCE		500 MG/BID	Transplacental	500 mg, bid	HIV infection		
9	INTELENCE		500 MG/QD	Transplacental	500 mg, QD			
10	INTELENCE		1000 MG/QID	Transplacental	1000 mg, qid	Antiretroviral therapy		
11	INTELENCE		1000 MG/QD	Transplacental	1000 mg, QD			
12	INTELENCE		1000 MG/Q6H	Transplacental	1000 mg, Q6H			
13	INTELENCE		1000 MG/QD	Transplacental	1000 mg, QD			
14	ISENTRESS		400 MG/BID	Transplacental	400 mg, bid	HIV infection		
15	ISENTRESS		400 MG/QD	Transplacental	400 mg, QD	HIV infection		
16	ISENTRESS					HIV infection		

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	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
17	NORVIR		100 MG/BID	Transplacental	100 mg, BID	HIV infection	(b) (6)	
18	NORVIR		200 MG/BID	Transplacental	200 mg, bid	HIV infection		
19	NORVIR		400 MG/BID	Transplacental	400 mg, BID			
20	NORVIR		400 MG/QD	Transplacental	400 mg, QD	HIV infection		
21	NORVIR			Transplacental	UNK, U			
22	NORVIR		200 MG/QD	Transplacental	200 mg, QD			
23	PREZISTA		600 MG/BID	Transplacental	1200 mg	HIV infection		
24	PREZISTA			Transplacental	UNK UNK, U	HIV infection		
25	RALTEGRAVIR		400 MG/QD	Transplacental	400 mg, QD	Product used for unknown indication		
26	TRUVADA			Transplacental	UNK			
27	ZIDOVUDINE			Transplacental				
28	ZIDOVUDINE			Transplacental	UNK	HIV infection		
29	ZIDOVUDINE			Transplacental	UNK			
30	ZIDOVUDINE			Transplacental	UNK, U			

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TRUVADA	377 Day	Yes	Unk				GILEAD	
2	APTIVUS	650 Day	Yes	Unk	UNKNOWN				
3	APTIVUS	650 Day	Yes	Unk	UNKNOWN				
4	APTIVUS	650 Day	Yes	Unk					
5	ETRAVIRINE	121 Day	Unk	Unk					

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	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler		OTC
6	ETRAVIRINE	121 Day	Unk	Unk						
7	INTELENCE	121 Day	Unk	Unk						
8	INTELENCE	121 Day	Unk	Unk						
9	INTELENCE	121 Day	Unk	Unk						
10	INTELENCE	121 Day	Unk	Unk	UNKNOWN					
11	INTELENCE	121 Day	Unk	Unk						
12	INTELENCE	121 Day	Unk	Unk						
13	INTELENCE	121 Day	Unk	Unk						
14	ISENTRESS	121 Day	Yes	Unk	UNKNOWN					
15	ISENTRESS	121 Day	Yes	Unk						
16	ISENTRESS	121 Day	Yes	Unk						
17	NORVIR	121 Day	Unk	Unk						
18	NORVIR	121 Day	Unk	Unk	UNKNOWN					
19	NORVIR	121 Day	Unk	Unk						
20	NORVIR	121 Day	Unk	Unk						
21	NORVIR	121 Day	Unk	Unk	UNKNOWN					
22	NORVIR	121 Day	Unk	Unk	UNKNOWN					
23	PREZISTA	121 Day	NA	NA						

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	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)	Start Date	End Date
	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
24	PREZISTA	121 Day	NA	NA	UNKNOWN				
25	RALTEGRAVIR		Unk	NA					
26	TRUVADA	377 Day	Yes	Unk	UNKNOWN			GILEAD	
27	ZIDOVUDINE		Unk	Unk	UNKNOWN				
28	ZIDOVUDINE		Unk	Unk					
29	ZIDOVUDINE		Unk	Unk	UNKNOWN				
30	ZIDOVUDINE		Unk	Unk	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Anal atresia	NA
Anencephaly	NA
Bladder agenesis	NA
Blood iron decreased	NA
Caudal regression syndrome	NA
Cloacal exstrophy	NA
Congenital anomaly	NA
Congenital ectopic bladder	NA
Congenital genital malformation	NA
Congenital musculoskeletal anomaly	NA
Erythema	NA
Exomphalos	NA
Fibrosis	NA

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Foetal exposure during pregnancy	NA
Gastrointestinal disorder congenital	NA
Gastrointestinal malformation	NA
Genitalia external ambiguous	NA
Lipodystrophy acquired	NA
Meconium stain	NA
Meningomyelocele	NA
Musculoskeletal discomfort	NA
Neural tube defect	NA
Premature baby	NA
Sepsis	NA
Spina bifida	NA
Spine malformation	NA
Tethered cord syndrome	NA
Umbilical cord abnormality	NA

Event/Problem Narrative:

Narrative as reported by MHRA (Ref. no: GB-MHRA-ADR 20548096): A spontaneous report received from a midwife, physician and pharmacist via the MHRA the APR (ref 071204) and JNJ (ref 20090908765) describes a female fetus who transplacentally received TVD. The patient's 42-year-old Black mother commenced TVD (1 DF, daily) on 05-JUN-2007 her concomitant medications included Aptivus, Ritonavir and prednisolone. On 03-JUN-2008, her ALT was 194. Her LMP was on (b) (6). On 19-JUN-2008, her antinuclear body was 1:400 and smooth muscle antibody was 1:1000. On (b) (6), at 18+ weeks gestation TVD and tipranavir were discontinued and mother was switched to another antiretroviral regimen due to adverse events consisting of increased daily dosage of ritonavir, Intelence, Isentress and Prezista. Medical history included HIV, gestational diabetes treated with Novarapid, renal vascular disorder NOS, STDs, systemic tuberculosis, increased ALT, increased AST, metabolic disorder and pulmonary TB. No history of alcohol, smoking or use of recreational drugs. She weighed 74kg. She was gravida 2 (including the current pregnancy), para 1 and 1 normal outcome (no spontaneous losses). No family history of congenital anomalies, significant outcomes or heredity disorders. She was not enrolled in a clinical study. On (b) (6), she discovered she was pregnant with an estimated due date of (b) (6). There were no relevant maternal risk factors in the home/work environment. On an unspecified date during pregnancy the mother experienced drug induced hepatitis for which blood and urine tests were carried out. The outcome for hepatitis was unk. An ultrasound scan of the fetus performed at week 11, 21 and 28 showed no abnormalities. On (b) (6), the mother gave birth to a live born female infant at 28 weeks gestation with spontaneous vertex meconium stained liquor

and NBM. The mother's viral load was less than 40. She received zidovudine and insulin aspart during birth. At birth, the patient weighed 2.5kg with a head circumference of 31cm. Labor was spontaneous with a vaginal delay of less than 40 with quick progress, no resuscitation was required for the baby. The umbilical cord snapped at birth and the baby was reported to have looked pale with an iron count of 10.4. It was reported that a blood transfusion (1 unit) was required upon delivery (2 in total). On the same day, raltegravir was stopped. The neonate presented with cloacal exstrophy, exomphalos, ambiguous small befid genitalia, absent anus, flat bottom (deficient lower spine), butterfly vertebral T11 anomaly, bilateral iliac osteotortis myelomeningocele (with low-lying spinal cord tethering), sacral agenesis (type 2), anal atresia, bladder agenesis, congenital genital malformation, gastrointestinal malformation, and muscle skeletal discomfort. Apgar testing results were 6 at one min, 8 at five min and both 10 and 6 were reported. On the same day, sepsis was negative in microbiology. Exposure in utero ended on this date and an MRI was due. Hemoglobin throughout admission was between 8.1 and 8.3 (thought to be affecting lethargy, feeds), HIV test was neg and ultrasound of the kidney was normal. It was reported that IV fluids were started. The patient was also started on IV AZT, Enfuvirtide, ritonavir, and was due to also start Darunavir (35 weeks). Penicillin & gentamen/metronidazole secondary to exomphalos were started and the patient also received bilateral iliac osteotomies surgery for the cloacal exstrophy. The patient developed a septic episode with pyrexia, lethargy and was feeding poorly. The right thigh/buttock was red and sore. Lipodystrophy & sepsis were also noted. A septic screen performed was negative. On an unspecified date, erythema developed. The patient was given cefotaxime, flucloxacilin, gentamicin and fluconazole for a 7-day course which showed clinical improvement with pyrexia settling. Post gentamicin level was reportedly raised at 9.3. The patient was reviewed by surgeons and was transferred to a specialist referral unit for neurosurgical, urological and orthopedic neonatal care with a discharge weight of 2280g. On an unspecified date, the patient recovered from sepsis, low iron count, erythema and exposure in utero, and the following events recovered with sequelae; spine malformation, tethered cord syndrome, omphalocele, musculoskeletal anomaly, muscle skeletal discomfort, myelomeningocele, genitalia external ambiguous, congenital genital malformation, meconium stain, bladder agenesis, anal atresia, cloacal exstrophy, sacral agenesis and umbilical cord abnormality. The event of premature baby was reported as not recovered and all other event outcomes were unknown. The physician stated that all adverse events had been repaired or resolved with surgery and the patient had recovered as much as possible. The reporter assessed all events to be serious (life-threatening, congenital anomaly, all disability/incapacity, hospitalisation and important medical event) and assessed the following treatments to be suspect drugs: TVD, etravirine, darunavir, raltegravir and ritonavir. No further information is expected. Case linked to mother case (MCN 2009-0025174). Information received on 18 -AUG-2009: No new information. Follow-up on 02-SEP-2009: Events added (Anomaly Congenital Musculoskeletal NOS, Flat Buttocks, Myelomeningocele and Sacral Agenesis) and events amended (was Genitalia External Ambiguous now Ambiguous External Genitalia; was Gastrointestinal Disorder Congenital now Gastrointestinal Disorder Congenital NOS & was Exomphalos now Omphalocele), pt DOB; gender & weight, TVD daily dosage, reporter seriousness (disability/incapacity & hospitalisation), relevant medical history not provided, spontaneous vaginal delay, no resuscitation, blood transfusion required (for mother or baby unk), and all events ongoing. This information has been incorporated into the case. Follow-up on 10-SEP-2009: Events added: Umbilical cord complication and Blood Iron Decreased, lab data, ritonavir amended from suspect to con med, blood transfusion clarification for baby, reporter assessment and bilateral iliac osteotomies surgery. This information has been incorporated into the case. Information on 18 -SEP-2009: No new information. Information on 02-NOV-2009. No new information. Information on 25 -NOV-2009. No new information. Information on 02-DEC-2009. No new information. Follow-up on 11-JAN-2010: Suspect drugs amended (etravirine, darunavir, raltegravir and ritonavir), mother con med added (insulin), TVD; tipranavir; ritonavir & raltegravir stop dates and events assessed as life threatening. This information has been incorporated into the case. Information on 13-JAN-2010: No new information. Information on 19-JAN-2010: No new information. On 08-FEB-2010 the

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MHRA informed Gilead that MCN 2009-0023512 was found to be a duplicate of MCN 2009-0025175. MCN 2009-0025175 has been deleted and all information has been incorporated into MCN2009-0023512 as will remain as the case of record. Case linked to mother case (events added (Anal Atresia, Bladder Agenesis, Congenital Genital Malformation and Gastrointestinal Malformation), APR documents, J&J ref, TVD start date amended, con med details amended, LMP amended, mother age, clinical indicators at start of pregnancy, mother not enrolled in clinical study, med info, mothers history, EDD and baby results/evolution (ultrasound, apgar, hb and HIV). Follow-up received on 26-FEB-2010: Events amended and added, seriousness criteria, con med details amended, apgar test results, sepsis negative in microbiology, mother black, first date mother seen during pregnancy, mother's med history, ultrasound date amended, sacral agenesis (type 2), and all outcomes of events are unk. Follow-up on 10-MAR-2010: Events seriousness (all disability/incapacity & hospitalisation), TVD & tipranavir start date amended, etravirine & ritonavir dosage and event outcomes amended. Follow-up on 15-MAR-2010: New event added (Congenital Anomaly, Gastrointestinal Malformation and Spinal Malformation), etravirine dosage amended and tipranavir date amended. Follow-up on 07-APR-2010: TVD start date amended again and con med details. Information on 19-APR-2010: No new information. Information on 12 May 2010: No new information. Information on 18 -JUN-2010: No new information. Information on 09-JUL-2010: No new significant information (MHRA confirmed that the mother commenced TVD on 05 Jun 2007). Information on 09-JUL-2010: No new information (MHRA updated the product section to confirm that TVD was commenced (by the mother) on 05 June 2007) for re-expediting. Information on 04-AUG-2010: No new sign. information (APR amended ref). Follow-up information on 09 -SEP-2010: New event (Erythema), events amended (Blood Iron Decreased to Iron Count was Low at 10.4, Exomphalos to Omphalocele, Gastrointestinal Disorder Congenital to Disorder Gastrointestinal Congenital, Genitalia External Ambigious to Genitalia External, Musculoskeletal Deformity to Musculoskeletal Anomaly), con med dose amendments, outcome for events and no further information is expected. 14-SEP-2009: Case E2B_00000833 was a duplicate of this case and case 2009-0025174 (mother and baby cases), the information has been incorporated into these cases and case E2B_00000833 has been deleted. Information on 17-SEP-2010: No new information. 22-SEP-2009: Case E2B_00000851 was a duplicate of this case and case 2009-0025174 (mother and baby cases), the information has been incorporated into these cases and case E2B_00000851 has been deleted. Information received on 30-SEP-2010: No new information. 14 -OCT-2010 Case E2B_00000876 was imported from the MHRA however it was a duplicate of this case and case 2009-0025174 (mother and baby cases). The information has been incorporated into these cases and case E2B_00000876 has been deleted. Update was received on 30 -AUG-2013: Cases 2009-023512 and 2013-0081320 were identified as duplicates. Case 2009-023512 was determined to be the master case and 2013-0081320 is the duplicate case. All future correspondence should be under case 2009-023512. Information from 2013-0081320 has been incorporated into 2009-023512 including the following: Event muscle skeletal discomfort added. Event genitalia external amended to genitalia external ambiguous. The outcome of the event exposure in utero was updated. Follow-up on 12-SEP-2013: Patient birth weight and gestational age added. Documents received from Merck on 06 Aug 2014 and from APR on 08 and 12 Aug 2014: No new information received. Documents received from MHRA on 08 and 10 Sep 2014: No new information. Documents from APR on 23 Sep 2014: No new information. Documents from MHRA on 09 and 16 Oct and 04 Nov 2014: No new information. Follow-up on 21 APR 2015: The APR reported the neonate's birth weight was 2200 g, gestational age at birth was 37, updated maternal event of gestational diabetes, the patient commenced treatment with TVD on 05 SEP 2006. The information reported by the MHRA (differs from APR) has been maintained in the case. The APR reported etiology for the birth defect of omphalocele, congenital genital malformation, the defect of bladder agenesis, the defect of cloacal exstrophy. Of note, to resolve an E2B transmission failure during the submission of case MCN 2009-0023512, this case (MCN 2015-0152641) was created. All information has been transferred and merged from case MCN 2009-0023512 to this case, and this case will remain the case of record. Additional information from the agency on 09-SEP-2010.

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On (b) (6) the baby had an APGAR score of 8 (at 5 min reported by the agency). The start date of therapy with tipranavir and TVD was corrected to 05-SEP-2006. The mother's experience is captured in WAES 0910GBR00060. Follow up from APR on 08-AUG-2014. Urine analysis of 29-AUG-2008 confirmed pregnancy. ALT on unk dates results reported as 800 units and 745 units. AST on unk date resulted increased. It has been determined that case # 0910GBR00060B1 is a duplicate of case # 1505GBR005321. Therefore, case # 0910GBR00060B1 is being deleted from our files and the cases are consolidated into case # 1505GBR005321. Follow up received on 21-APR-2017 from MHRA. Lab values were provided. Current condition of HIV was reported. Start date for the congenital anomaly was reported as 21-FEB-2009. The following events were added: Congenital musculoskeletal anomaly/musculoskeletal deformity was serious (medically significant) with outcome of resolved. Spina bifida, Anencephaly, Exstrophy of the bladder, Neural tube defects and Congenital musculoskeletal anomaly were serious (medically significant) with outcomes of unk. Action taken with TVD was drug discontinued. Follow up received on 05-MAY-2017 from MHRA. Additional maternal history provided. Dosing for two concomitant medications were provided. Follow up received 14-JUN-2017 by MHRA and 24-JUL-2017 by Gilead. The parents LMP was (b) (6). Action taken with NORVIR was updated to NOT APPLICABLE. Follow up received on 24-AUG-2017, 28-AUG-2017 and 31-AUG-2017 from MHRA. All reports were processed together along with a non-significant case correction. Updated parent medical history and dosing for co suspect medications: Aptivus, Norvir, Isentress and Etravirine. Case correction: As reported causality for the event tethered cord syndrome has been updated to related. Assessment of listedness for the Core label for the AE of Musculoskeletal discomfort has been updated. Follow-up on 01 and 08-Sep-2017 from MHRA. No new information. Follow-up from MHRA on 14-SEP-2017. TVD & TIPRANAVIR (APTIVUS) were discontinued on 23-OCT-2008 (second trimester). Additional maternal history provided including: Aspartate aminotransferase increased and pulmonary TB (start date 1993). The following events were serious (medically significant, hospitalization, congenital anomaly, disability, and life-threatening): cloacal exstrophy, spine malformation, omphalocele, meningomyelocele, congenital gastrointestinal disorder, congenital genital malformation, bladder agenesis, anal atresia, sacral agenesis, gastrointestinal malformation, musculoskeletal anomaly, genitalia external, meconium stain, umbilical cord abnormality, tethered cord syndrome, congenital anomaly, lipodystrophy acquired, erythema, iron count was low at 10.4, anencephaly, and neural tube defect. follow-up from MHRA on 19-SEP-2017. The outcome for event congenital gastrointestinal disorder was updated from unk to resolved with sequelae. Follow-up from MHRA on 29-SEP and 03-OCT-2017. No new information. Follow-up from MHRA on 10-OCT-2017. The gestational age was updated to 37 weeks to match with the LMP date and delivery date already reported. Follow-up from MHRA on 12 and 26-OCT-2017. No new information. Follow-up from EMA (GB-EMA-DD-20180426-devashreeevhpdd-113444) on 30-APR-2018. ZIDOVUDINE was changed to suspect drug. Additional INTELENCE dosage regimen: 1000 mg, QD, transplacental from an unk date to 23-OCT-2018 and 500 mg, QD, transplacental from an unk date to an unk date. Additional ISENTRESS dosage regimen: 400 mg, QD, transplacental from an unk date to an unk date. Additional NORVIR dosage regimen: 400 mg QD, transplacental from an unk date to an unk date. Start date of NORVIR 200mg, QD; APTIVUS & TVD 1DF, QD was changed to 16-JUN-2008. Additional con meds: INSULIN & TIPRANAVIR. Action taken with APTIVUS was changed to unk. Follow-up was received from RA-EMA (GB-009507513-0910GBR00060/GB-MERCK-0910GBR00060; GB-MERCK-1505GBR005321/GB-MHRA-ADR 20548096) on 24-JUL-2018. The event of drug exposure in utero was changed to drug exposure in utero/ second trimester. The event was assessed as serious. The events of MUSCLE SKELETAL DISCOMFORT and PREMATURE BABY/premature birth were updated from non-serious to serious. The outcome of the events of GASTROINTESTINAL DISORDER CONGENITAL/CONGENITAL GASTROINTESTINAL DISORDER and CONGENITAL GENITAL MALFORMATION /GENITAL MALFORMATION was changed to resolved with sequelae. Additional dosage regimen for INTELENCE: 1000 mg, q6h, transplacental. Additional dosage regimen for Norvir 400 mg, bid, transplacental. From EMA on 03-AUG-2018(3 reports). No new

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information. Follow-up on 20-AUG-2018 from RA-EMA (GB-MHRA-ADR 20548096; GB-MERCK-1050GBR005321). Raltegravir added suspect medication. Follow-up from RA-EMA (GB-ViiV Healthcare Limited-A1041735A) on 29-AUG-2018. The event of unspecified disease of fibrous tissue [fibrosis] was added. Fibrosis was serious (life threatening, medically significant, congenital anomaly, hospitalized, disability) with an outcome of unknown. LIPODYSTROPHY ACQUIRED was updated to LIPODYSTROPHY ACQUIRED/flat buttocks/flat buttocks.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Antiretroviral therapy			YES
Exposure to communicable disease			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture	Negative	N/A			Y
Iron	10.4	Unknown			N
Ultrasound antenatal screen	no defects at 211 weeks unknown	N/A			N
Cranial ultrasound scan	No abnormalities detected	N/A			N
Urine analysis	pregnancy confirmed unknown	Unknown			N
Apgar score	10 at 5 minutes	N/A			N
Alanine aminotransferase	800	Unknown			N
Apgar score	6 at 1 minute	N/A			N
Ultrasound kidney	Normal	N/A			N

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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	745	Unknown			N
Ultrasound scan	Full test results in relevant tests	N/A			N
Weight	2.2	kg			N
Weight	2200	g			N
Head circumference	31 cm	Unknown			N
Hemoglobin	between 8.1 and 8.3	Unknown	8.1	8.3	N
Microbiology test	sepsis - negative microbiology	N/A			N
Apgar score	8 at 5 minutes	N/A			N
Blood HIV RNA	Negative	N/A			N
Culture	Negative	N/A			Y
Ultrasound antenatal screen	no defects at 22 weeks unknown	N/A			N
Weight	2.5	kg			N
Weight	2.28	kg			Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ENFUVIRTIDE		Transplacental	UNK				
2	ENFUVIRTIDE	25 MG/	Unknown	25 mg, UNK	Product used for unknown indication			
3	INSULIN				Gestational diabetes			
4	NITROUS OXIDE		Transplacental	UNK				
5	NITROUS OXIDE		Unknown	UNK				
6	NITROUS OXIDE		Transplacental	UNK	Product used for unknown indication			
7	NITROUS OXIDE		Unknown	UNK				
8	NITROUS OXIDE		Transplacental	UNK				
9	NITROUS OXIDE		Unknown	UNK				

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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
10	NITROUS OXIDE		Unknown	UNK				
11	NITROUS OXIDE		Transplacental	UNK				
12	NITROUS OXIDE	25 MG/	Transplacental	25 mg, UNK				
13	NITROUS OXIDE	25 MG/	Transplacental	25 mg, UNK				
14	NITROUS OXIDE		Unknown	UNK				
15	NOVORAPID	200 MG/BID	Transplacental	200 mg, BID	Gestational diabetes			
16	NOVORAPID			UNK				
17	OXYGEN		Transplacental	UNK				
18	OXYGEN		Transplacental	UNK	Product used for unknown indication			
19	PREDNISOLONE	25 MG/	Transplacental	25 mg, UNK	Product used for unknown indication			
20	PREDNISOLONE		Transplacental	UNK				
21	PREDNISOLONE		Transplacental	UNK				
22	TIPRANAVIR				Exposure during pregnancy			
23	TIPRANAVIR				Exposure during pregnancy			

Reporter Source:

Study Report?: No

Sender Organization: GILEAD

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 11225746

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** FRA **Event Date:** 01-May-2015 **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 28-Jan-2016 **Mfr Rcvd Date:** 19-Jan-2016 **Mfr Control #:** FR-MERCK-1506FRA011547 **Application #:** 205786

Patient Information:

Age: < 1 DAY **Sex:** Male **Weight:** KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ISENTRESS			Transplacental				
2	NORVIR			Transplacental				
3	PREZISTA			Transplacental				
4	TRANDATE			Transplacental				

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ISENTRESS		NA	NA				MERCK	
2	NORVIR		NA	NA					
3	PREZISTA		NA	NA					
4	TRANDATE		NA	NA					

Event Information:

Preferred Term (MedDRA Â© Version: 21.0)	ReC
Aqueductal stenosis	NA
Foetal exposure during pregnancy	NA
Hemivertebra	NA
Microtia	NA
Multiple congenital abnormalities	NA

Premature baby	NA
Spinal disorder	NA
Synostosis	NA
Tracheo-oesophageal fistula	NA

Event/Problem Narrative:

This spontaneous report as received via the French Health Authority (NT20150536) refers to a male new born patient born to a 28 year old female patient. The patient's mother had Human Immunodeficiency Virus (HIV) undetectable viral load under antiretroviral bitherapy and Chronic arterial hypertension.

On an unknown date, the patient's mother started therapy with raltegravir potassium (ISENTRESS) (formulation, strength, LOT# not reported), ritonavir (NORVIR) (formulation, strength, route of administration, LOT# not reported), darunavir (PREZISTA) orally (formulation, strength, LOT# not reported), and labetalol hydrochloride (TRANDATE) (formulation, strength, LOT# not reported) for unknown indication. The child's mother became pregnant with a last menstrual period (LMP) of (b) (6) and Estimated Date of Delivery(EDD) of (b) (6) Gravida and para were reported as 1.

On an unknown date, the child was diagnosed with multiple congenital abnormalities (congenital anomaly). The patient's mother had a spontaneous pregnancy, reported as natural, marked by an antenatal diagnosis of multiple malformation syndrome, associating with ventriculomegaly and an abnormality of the median line, a suspected esophageal atresia, suspected ventricular septal defect, hemi-vertebrea and hydroaminosis. Premature rupture of the amniotic sac occurred on (b) (6) at 36 week amenorrhea+4 days. Induction of Labor was at 37 weeks amnenorrhea+4 days. On (b) (6), caesarian section was performed under epidural due to a stagnation of fetal growth, with presentation in the top part (mother case MARRS# (b) (6)). Bad adaptation to extrauterine life, with Apgar at 5 then 9 with prolonged cyanosis requiring nasopharyngeal aspiration and balloon ventilations. Birth weight of the newborn was 2.5 kg (10th percentile), cranial perimeter at 35 cm (between 50th percentile and 90th percentile), and height at 46 cm (10th percentile).
At the level of multiple malformation syndrome examination, a transfontanellar ultrasound was performed and found a ventricular system in place clearly dilated with a tri-ventricular hydrocephalus with a 4th non dilated ventricle and septal agenesis. No intra-ventricular hemorrhage; normal cerebral parenchyma, and corpus callosum present and thin, integrity of the cerebellum. A Nuclear magnetic resonance imaging (MRI) was performed on (b) (6), which confirmed abnormality with a normal aspect of the brain stern and cerebellum and normal gyration for age. An MRI of control was performed on (b) (6), which found a stability of tri-ventricular dilatation with ventricular crossroads measured at 28 cm, without transependymal resorption, and short stenosis of 6 mm of Sylvius aqueduct and a 4th normal ventricle. In total an aspect in favor of aqueduct stenosis. The optic chiasm seemed integrate. Electroencephalogram (EEG) found the absence of pathological picture and normal tracing for the term. Esophageal transit found atresia of esophagus with cul de sac at the height of T6-T7. Abdomino, pelvic and medullar ultrasound was without particularities. Heart ultrasound was normal. Eye fundus examination was without particularities. Visual evoked potential tests using a checkerboard were not obtained. Flash visual evoked potential tests were deteriorated in favor of

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bilateral optic tracts damage Spine X-ray of face and profile found lumbar hemi vertebras and cervical butterfly vertebra (spinal disorder) associated with coastal anomalies (bilateral costal synostosis). On clinical state, the infant presented with a malformed right ear without ear canal (microtia). A computerized tomogram (CT) scan of petrous part of temporal bone and facial mass found aplasia of the right external auditory canal with absence of the handle of the Malleus. No malformations of the right inner ear. At left, a partial filling antra-mastoiditis and middle ear without suspicious opacity. No malformations of the left inner ear. Auditory evoked potentials were absent on the right, and present at left but poorly designed. The outcome of the event multiple malformations was reported as not recovered.

The French Health Authority coded multiple malformations as a serious adverse event, checked congenital anomaly as serious criterion and considered it to be related to therapy raltegravir potassium (ISENTRESS), ritonavir (NORVIR), darunavir (PREZISTA) and labetalol hydrochloride (TRANDATE)

Follow up information has been received from the Antiretroviral Pregnancy Registry for raltegravir potassium (ISENTRESS), a Pregnancy Registry product, on 31-JUL-2015.

APR Registry mother ID and the APR Baby ID are (b) (6) and (b) (6) respectively.
It was reported that the patient was born premature on (b) (6) (also reported by source that the gestational age was 37). On an unknown date the patient had experienced multiple congenital abnormalities such as hydrocephalus/aquaductal stenosis, esophageal atresia without tracheoesophagea, malformed right ear with no auditory canal, lumbar hemivertebrae, cervical butterfly vertebrae, costal synostosis on both sides, malformed right ear with no auditory canal. Birth defect contributing factors were reported as unknown.

Supplemental information received from the APR on 05-AUG-2015 provided the birth defect evaluator's assessment.
The etiology for the event hydrocephalus/aquaductal stenosis was reported as the cerebral aqueduct connects the third and fourth ventricles. In adults it is 1.1 cm long. Obstruction of the aqueduct may be primary, or there may be secondary compression or internal blockage.

The etiology for the event costal synostosis on both sides was reported as this probably goes with the vertebral anomalies, though no mention is made in the report of thoracic vertebral involvement. The ribs are elongated processes off of the thoracic vertebrae. The pattern and hydrocephalus results from blocked circulation of csf. Temporality was hard to assess, even in cases with clear medication exposure times.

The etiology for the event esophageal atresia without tracheoesophagea was reported as the esophagus is formed during early infolding that creates the gut tube. Separated from the
trachea at 4 weeks post conception. It is hypothesized that atresia results when insufficient endoderm.

The etiology for the event malformed right ear with no auditory canal was reported as microtia consists of malformation of the auricle. For the purposes of MACDP it also includes
stricture or atresia of the external auditory canal. There is a wide spectrum of this defect and the remains with the esophagus when it separates from the trachea. And is heterogeneous It is a common defect occurring 11500- 1/3000 live births. It is twice as common in males.

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About 20% of patients with microtia have a defined syndrome. The ears form in weeks 6-8.

The etiology for the event lumbar hemivertebrae was reported as segmentation anomalies of the vertebrae are disorders of primary somitogenesis in the very early embryo.

The etiology for the event cervical butterfly vertebrae was reported as segmentation anomalies of the vertebrae are disorders of primary somitogenesis in the very early embryo.
The birth defect evaluator did not assess the temporality for the events.

Upon internal review the event of Premature baby was considered to be medically significant.
It was unknown if the events were attributed to the suspect therapies. This report was linked to 1506FRA013463 as parent-child link.

Follow up information has been received via French Health Authority (NT20150536) on 04-NOV-2015.
The clinical picture was evocative of VACTERL syndrome. The patient underwent surgery for esophageal atresia type III and brain triventricular dilatation associated with right anotia and cervical hemivertebrae.

Follow up information has been received for the Antiretroviral Pregnancy Registry (from a health care professional) on 10-DEC-2015. The causality for the events of multiple congenital abnormalities, premature baby, cervical butterfly vertebrae, hemivertebra, malformed right ear without ear canal, oesophageal atresia, synostosis and hydrocephalus/aqueductal stenosis was unknown. There was not defect reported and there was not postnatal problem reported. It was also reported that the exposure to medication were prior to conception (date unspecified). Event's causality and narrative were updated.

Follow up information was received on 19-JAN-2016 for the Antiretroviral Pregnancy Registry from the a health care professional. It was reported that the physical symptoms were compatible with vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies and limb abnormalities (VACTERL) association.
The patient underwent type III esophagus atresia surgery and brain ventricular enlargement of 3 ventricles associates with right and hemi vertebrae cervical anotia.
It was unknown if the defects were attributed to Antiretroviral (ARV) therapy and unknown if other factors contributed to the outcome.

List of defects provided was: Vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies, limb abnormalities, hydrocephalus and anotia. The vertebral defects, hydrocephalus and anotia were accounted for in the previous defect list. The trachea-esophageal fistula was previously reported as esophageal atresia had been modified. The other defects were not found in the patient: the were listed out as the spelled-out versions of a possible unifying diagnosis and mistakenly reported in the reporter form as being present. No previously reported defects were deleted.

Additional information will be provided if available.

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Events and narrative were updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Ultrasound abdomen	no particularities	N/A			N
Face X-ray	found lumbar hemi vertebras and cervical butterfly	N/A			N
Ultrasound scan	normal	N/A			N
Ultrasound foetal	found a ventricular system in place clearly dilate	N/A			N
Electroencephalogram	found the absence of pathological picture and norm	N/A			N
Computerised tomogram	found aplasia of the right external auditory canal	N/A			N
Nuclear magnetic resonance imaging	found a stability of tri-ventricular	N/A			N

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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Ultrasound pelvis	dilation with no particularities	N/A			N
Ultrasound scan	no particularities	N/A			N
Fundi examination	no particularities	N/A			N
Nuclear magnetic resonance imaging	confirmed abnormality with a normal aspect of the	N/A			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: MERCK

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 11275144

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** PRI **Event Date:** **Outcomes:** CA,DE,OT, **Application Type:** NDA

FDA Rcvd Date: 09-Aug-2018 **Mfr Rcvd Date:** 14-Jun-2018 **Mfr Control #:** PR-009507513-1507PER007282 **Application #:** 022145

Patient Information:

Age: **Sex:** Male **Weight:** .08 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	RALTEGRAVIR POTASSIUM		800 MG/QD	Transplacental	800 mg, qd			
2	INTELENCE		400 MG/QD	Transplacental	400 mg, qd			
3	TRUVADA		1 DF/QD	Transplacental	1 tab/caps, qd			

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	RALTEGRAVIR POTASSIUM		NA	NA				MERCK	
2	INTELENCE		NA	NA					
3	TRUVADA		NA	NA					

Event Information:

Preferred Term (MedDRA Â Version: 21.0)	ReC
Encephalocele	NA
Foetal exposure during pregnancy	NA
Single umbilical artery	NA

Case ID: 11275144

Event/Problem Narrative:

Information has been received for the Antiretroviral Pregnancy Registry from a healthcare professional concerning a male fetus, weight 83 grams.
Patient's mother was a 39 years old Hispanic female patient (mother APR# (b) (6) and baby APR# (b) (6)) with hepatitis C (Worst Disease Severity Indicator (by history) of Hepatitis C was reported as "Compensated liver disease (Pugh score <7)") and human immunodeficiency virus (HIV)infection (Worst Disease Severity Indicator (by history) of HIV was reported as "Asymptomatic, acute (primary) HIV or PGL (persistent generalized lymphadenopathy)").
The patient's mother's medical history included abortion spontaneous.

On an unknown date, the patient's mother started therapy with raltegravir potassium (ISENTRESS) tablets, 800 mg, qd, course 1, for HIV infection and hepatitis C. Other suspect therapies included emtricitabine (+) tenofovir disoproxil fumarate (1 tablet daily, oral, course 1) and etravirine (INTELENCE) (400 mg daily, oral, course 1) both started on an unspecified date. Earliest CD4+ T cell category in this pregnancy was 200-499 cells/microL (test date was not provided). The patient's mother was pregnant with date of last menstrual period (LMP) of (b) (6) and estimated date of delivery (EDD) on (b) (6).
The patient's mother was placed on these therapies at conception. On (b) (6), the patient's mother had spontaneous abortion at gestational age of 17 weeks. The baby's birth defect including encephalocele and 2 vessel cord was noted.
Therapy with raltegravir potassium(ISENTRESS), emtricitabine (+) tenofovir disoproxil fumarate and etravirine (INTELENCE) was continued.
Causality for encephalocele and 2 vessel cord was reported as not related to raltegravir potassium (ISENTRESS), emtricitabine (+) tenofovir disoproxil fumarate and etravirine (INTELENCE).

Additional information received from the APR on 18-JUL-2015 provided the birth defect evaluator's assessment. The birth defect evaluator considered that possible association between encephalocele, 2 vessel cord and suspect therapy cannot be rule out. A cephalocele is herniation of cranial contents through a skull defect. An encephalocele is one that contains brain, most are occipital. 2 vessel cord occurs in about 1/200 newborns. There is increased incidence in twins. The missing artery either fails to form or degenerates early in development.

Follow up information has been received for the Antiretroviral Pregnancy Registry from a healthcare professional on 27-JUL-2015. Patient' s symptoms were presented before the birth and there was not family history of birth defects. There was no description about the birth defect. It was also reported that the patient's mother had two previous pregnancies and one of them was a spontaneous abortion (gravida 3, para 1) and that she had a concurrent condition of chlamydia.

This case is linked with maternal case (MARRS # 1508PRI002633).

Additional information is not expected because the case was closed with outcome.

This is an amended report. The previous E2B submissions for this safety report ÂPR-009507513-1507PER007282Â to your agency used incorrect E2B Linked report ÂPE-009507513-1508PRI002633Â. However, the correct E2B Linked report is ÂPR-009507513-1508PRI002633Â.

Case ID: 11275144

Follow up information has been received for the Antiretroviral Pregnancy Registry from a healthcare professional on 14-JUN-2018. The assessment was updated.
Company Causality Assessment: Based on the limited information currently available for this case, a reasonable possibility to suggest a relationship between raltegravir potassium therapy and the reported events of encephalocele and single umbilical artery cannot be established. Additional information such as complete raltegravir therapy details (including exact start date), complete maternal medical history, family history (including family history of neural tube defects), maternal concomitant medications, maternal social history, relevant labs/diagnostics and pregnancy course (including folic acid intake) is essential for a proper assessment.

Company Comment- No changes to the product safety information are warranted at this time. Merck and Co., Inc., Kenilworth, N.J., USA, known as MSD outside of the US and Canada, continues to monitor the safety profile of the product.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** MERCK **503B Compounding Outsourcing Facility?:**

Case ID: 11275144

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 12103690

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 17-Jul-2018 **Mfr Rcvd Date:** 14-Jun-2018 **Mfr Control #:** US-009507513-1602USA010104 **Application #:** 022145

Patient Information:

Age: **Sex:** Female **Weight:** KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ISENTRESS			Transplacental	UNK	HIV infection		
2	ISENTRESS					Hepatitis C		
3	TRUVADA			Transplacental	UNK	HIV infection		
4	TRUVADA					Hepatitis C		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ISENTRESS		Unk	NA				MERCK	
2	ISENTRESS		Unk	NA				MERCK	
3	TRUVADA		Unk	NA					
4	TRUVADA		Unk	NA					

Event Information:

Preferred Term (MedDRA Â Version: 21.0)	ReC
Hydrocephalus	NA
Meningomyelocele	NA
Neural tube defect	NA

Case ID: 12103690

Event/Problem Narrative:

Information has been received for the Antiretroviral Pregnancy Registry (Registry ID: (b) (6)) from a healthcare professional concerning an approximately 2 month old White female infant patient whose mother (Registry ID: (b) (6) was enrolled in "Antiretroviral Pregnancy Registry".

The patient's concurrent condition includes were not reported. Concomitant therapies included cefazolin sodium (ANCEF), acetaminophen, hydrocodone bitartrate (NORCO), docusate sodium (COLACE), simethicone (MYLICON), ledipasvir, sofosbuvir (HARVONI) and valacyclovir hydrochloride (VALTREX).

On an unknown date, the patient's mother started therapy with raltegravir potassium (ISENTRESS) (dose, strength and formulation: unknown) for HIV infection and hepatitis C. Other suspect therapies included emtricitabine, tenofovir disoproxil fumarate (TRUVADA) (dose, strength and formulation: unknown) started on 01-DEC-2012 for HIV infection and hepatitis C. On an unknown date, the patient's mother became pregnant (drug exposure during pregnancy) (MARRS # 1602USA009856).

On an unknown date, neural tube defect was noted prenatally, dating was not provided. The signs and symptoms were noted before birth. Prenatally, on an unspecified date, ultrasound showed that the baby had lower lumber and sacral lumber open neutral tube defect (Myelomeningocele with hydrocephalus) (congenital anomaly). On (b) (6), neonate born with congenital abnormalities (hydrocephalus and myelomeningocele). On (b) (6), she underwent ventriculoperitoneal shunt and myelomeningocele repair. On (b) (6), she was in stable condition post repair. Action taken was unknown. The outcome of hydrocephalus, neural tube defect and meningomyelocele was unknown. The reporter combined the two defects. Per reporter, they are considered a single item. Spina bifida and anencephaly occur by 28 days after conception as a failure of neural tube to close completely. Spina bifida of the myelomeningocele type is usually associated with backwards displacement of the cerebellum and posterior portion of the brain (Achiari malformation) which then results in hydrocephalus. There is a known association with maternal folic acid deficiency. Neural tube defect, such as myelomeningocele are the second most prevalent congenital abnormality and the majority as thought to be isolated malformations of multi factional origin (genetic and environmental factors). Majority of the patients with myelomeningocele have hydrocephalus. The reporter considered hydrocephalus, neural tube defect and meningomyelocele to be related to raltegravir potassium (ISENTRESS) and emtricitabine, tenofovir disoproxil fumarate (TRUVADA). The reporter could not rule out a possible association and birth defects were attributed to therapy with raltegravir potassium (ISENTRESS) and emtricitabine, tenofovir disoproxil fumarate (TRUVADA), other birth defects contributing factors were unknown.

Follow up information has been received from the healthcare professional on 23-FEB-2016. On 01-DEC-2012, the patient's mother started therapy with raltegravir potassium (ISENTRESS) (total daily dose and route of administration unknown). No further information provided regarding the events. No change in previous clinical evaluation.

Follow up information was received from healthcare professional on 29-JUL-2016. The prenatal test ultrasound which resulted in neural tube defect was performed on (b) (6). The report type was changed from report from study to spontaneous.

Follow-up information has been received from healthcare professional on 14-JUN-2018.

The patientÂs mother CD4 count at the start of pregnancy was reported as greater than 500?l. It was reported that, the patient's mother was exposed to all the suspect therapies at the time of conception. The gestational age at the time of delivery was reported as 37 weeks. The baby(patient) weight was reported as 2581 grams.

Case ID: 12103690

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ANCEF			UNK				
2	COLACE			UNK				
3	HARVONI			UNK				
4	MYLICON			UNK				
5	NORCO			UNK				
6	VALTREX			UNK				

Reporter Source:

Study Report?: No

Sender Organization: MERCK

503B Compounding Outsourcing Facility?:

Literature Text:

Case ID: 13264782

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** NAM **Event Date:** **Outcomes:** OT, **Application Type:** NDA

FDA Rcvd Date: 23-Feb-2017 **Mfr Rcvd Date:** 25-Jan-2017 **Mfr Control #:** NA-VIIV HEALTHCARE LIMITED-NA2017GSK023909 **Application #:** 204790

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Tivicay			Transplacental	UNK	HIV infection		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Tivicay		NA	NA				VIIV	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Foetal exposure during pregnancy	NA
Neural tube defect	NA

Event/Problem Narrative:

This retrospective pregnancy case was reported by a physician via sales rep and described the occurrence of neural tube defect in a patient exposed to dolutegravir (Tivicay) film-coated tablet in utero. The mother received the product for hiv infection.

On an unknown date, the 40-year-old mother started Tivicay (oral) at an unknown dose and frequency. The mother's last menstrual period was on an unknown date and estimated date of delivery was on an unknown date. Tivicay was continued with no change. The patient was diagnosed with neural tube defect (serious criteria GSK medically significant) and drug exposure in utero. On an unknown date, the outcome of the neural tube defect and drug exposure in utero were unchanged.

It was unknown if the reporter considered the neural tube defect to be related to Tivicay.

Additional details,
This patient had been on Tivicay treatment since a few months before falling pregnant and remained on Tivicay during the past few weeks of

Case ID: 13264782

pregnancy. The patient would be going to South Africa soon to had the baby brought down (termination of pregnancy). The Initial case exposure during pregnancy was apparently reported to the Care Accounts Manager in Namibia on 25 Jan 2017 and failed to report the case to them.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** VIIV **503B Compounding Outsourcing Facility?:**

Case ID: 13264782

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14567908

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BRA **Event Date:** **Outcomes:** CA,OT, **Application Type:** ANDA

FDA Rcvd Date: 06-Apr-2018 **Mfr Rcvd Date:** 12-Feb-2018 **Mfr Control #:** BR-MYLANLABS-2018M1012363 **Application #:** 204005

Patient Information:

Age: **Sex:** Male **Weight:** 2.92 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LAMIVUDINE/ZIDOVUDINE		900 MG/QD	Transplacental	900 mg, qd	Product used for unknown indication	05-Apr-2017	10-Aug-2017
2	ISENTRESS		400 MG/QD	Transplacental	400 mg, qd	Product used for unknown indication	05-Apr-2017	10-Aug-2017
3	MARIJUANA				3 Times per week	Product used for unknown indication		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LAMIVUDINE/ZIDOVUDINE		NA	NA					
2	ISENTRESS		NA	NA				MYLAN	
3	MARIJUANA		NA	NA				MYLAN	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Congenital skin dimples	NA
Foetal exposure during pregnancy	NA
Spina bifida	NA

Case ID: 14567908

Event/Problem Narrative:

Post Market. Survey report received on 12-Feb-2018.

This case, received from other health professional in Brazil, involved a neonate male patient who was reportedly exposed to Lamivudine, Zidovudine and non-company suspects raltegravir potassium and Cannabis sativa during gestation and experienced congenital skin dimples, spina bifida.

Medical history and concomitant medication were not reported.

Current condition (patientÂs mother) included HIV infection.

Non-company suspect medication included Isentress (raltegravir potassium) and Marijuana (Cannabis sativa).

Unknown date:The patient initiated Marijuana (Cannabis sativa) (3 Times per week) for an unknown indication.

05-Apr-2017: The patient initiated Lamivudine, Zidovudine (900 mg, qd, transplacental) and Isentress (raltegravir potassium) (400 mg, qd, transplacental) for an unknown indication.

10-Aug-2017: Patient took the last dose of Lamivudine, Zidovudine and Isentress (raltegravir potassium).

Unknown date: The patient had Small sacral dimple (Sacral dimple congenital and Spina bifida)

Outcome of events congenital skin dimples and spina bifida were unknown.

02-Mar-2018: Following internal review, a significant correction was performed for the information received on 12-Feb-2018. The need for correction was identified on 02-Mar-2018. Patient DOB updated, reference number added and narrative updated.

05-Apr-2017: The mother of patient initiated Lamivudine, Zidovudine (900 mg, qd, transplacental) and Isentress (raltegravir potassium) (400 mg, qd, transplacental) for an unknown indication.

Company Comment:
Serious: congenital skin dimples, spina bifida and are unlisted whereas foetal exposure during pregnancy (Non-serious) is listed as per the company RSI of Lamivudine, Zidovudine. Causality of the reported events assessed as possible as the contributory role of suspect drug cannot be completely excluded with available information. The non-Mylan co-suspect raltegravir potassium, Cannabis sativa and patients (mother) underlying medical condition (HIV) are the confounding risk factors.

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14567908

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** MYLAN **503B Compounding Outsourcing Facility?:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14686667

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 29-Oct-2017 **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 27-Mar-2018 **Mfr Rcvd Date:** 21-Mar-2018 **Mfr Control #:** US-GILEAD-2018-0328964 **Application #:** 207561

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE		1 DF/QD	Transplacental	1 DF, QD	HIV infection	13-Oct-2016	16-Dec-2017
2	EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE		1 DF/QD	Transplacental	1 DF, QD	HIV infection	16-Dec-2017	
3	ISENTRESS		1 DF/BID	Transplacental	1 DF, BID	HIV infection	16-Dec-2017	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE	512 Day	Unk	NA				GILEAD	
2	EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE	83 Day	Unk	NA				GILEAD	
3	ISENTRESS	83 Day	Unk	NA					

Event Information:

Preferred Term (MedDRA Â Version: 21.0)	ReC
Anencephaly	NA
Foetal exposure during pregnancy	NA

Case ID: 14686667

Event/Problem Narrative:

This case, manufacturer control number 2018-0328964 is a report received via the Antiretroviral Pregnancy Registry (APR) (Mother's Registry ID (b) (6))
referring to fetal patient whose mother was a 34-year-old Female of African descent. The investigator reported the following events: anencephaly and Drug exposure in utero for this case.

Historical condition:

Medical history: The mother's last menstrual period (LMP) was on (b) (6). The mother was first seen during this pregnancy on 06-FEB-2018. Her corrected date of delivery was (b) (6). The mother was HIV infected with a CD4 + T-Cell Category of greater or equal to 500 uL . Mother's HIV Severity Indicator was Asymptomatic, acute (primary) HIV or PGL (persistent generalized lymphadenopathy).

Historical drug: None Reported

From 13-OCT-2016 to 16-DEC-2017, the patient received oral ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE 1 DF (dose form), QD (daily) for treatment of HIV infection. On 16-DEC-2017, the patient received oral EMTRICITABINE, TENOFOVIR DISOPROXIL FUMARATE, 1 DF QD for HIV Infection.

Non-manufacturer co-suspect medications included oral Isentress, started on 16-DEC-2017 at 2 DF twice daily for HIV infection.

Concomitant medications were not reported by the investigator.

On 29-OCT-2017 , the patient experienced Drug exposure in utero.

On (b) (6), a prenatal ultrasound showed no defects.

On (b) (6), a prenatal ultrasound showed anencephaly.

Relevant laboratory/diagnostic tests included:

(b) (6), Ultrasound antenatal screen, No Defect detected

(b) (6), Ultrasound antenatal screen, ANENCEPHALY

Action taken with ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE, EMTRICITABINE, TENOFOVIR DISOPROXIL FUMARATE, and Isentress Unknown.

Case ID: 14686667

Anencephaly Serious (Medically significant, Congenital Anomaly) with an outcome of Not Reported

Drug exposure in utero was Non-Serious with an outcome of Not Reported

Initial report was received on 21-MAR-2018.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Ultrasound antenatal screen	No Defect detected	Unknown			N
Ultrasound antenatal screen	ANENCEPHALY	Unknown			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** GILEAD **503B Compounding Outsourcing Facility?:**

Case ID: 14686667

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882044

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BWA **Event Date:** 16-Oct-2017 **Outcomes:** CA,DE,OT, **Application Type:** NDA

FDA Rcvd Date: 02-Aug-2018 **Mfr Rcvd Date:** 25-Jul-2018 **Mfr Control #:** US-VIIV HEALTHCARE LIMITED-BW2018GSK083088 **Application #:** 204790

Patient Information:

Age: < 1 DAY **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Dolutegravir			Transplacental	UNK	HIV infection	01-Jun-2016	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Dolutegravir	502 Day	NA	NA				VIIV	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Anencephaly	NA
Foetal exposure during pregnancy	NA

Event/Problem Narrative:

This retrospective pregnancy case described the occurrence of anencephaly in a 39-week-old infant. The mother was a subject enrolled in an open label study titled Dolutegravir Non-GSK study. The subject received dolutegravir from 1st June 2016.

Concomitant product exposures included iron + folate.

The infant was exposed to dolutegravir during the first, second and third trimesters of pregnancy.

The infant was diagnosed with anencephaly. Serious criteria included death, GSK medically significant and congenital anomaly. Additional event(s) included drug exposure in utero. The outcome of anencephaly was fatal on (b) (6). The infant died on (b) (6). The reported cause of death was anencephaly.

It was unknown if the investigator considered the anencephaly to be related to dolutegravir.

Case ID: 14882044

Additional information:
The Tsepamo study (R01HD080471) is an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and (2) to determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. The study is powered to detect at least a 2-fold increase in the risk of NTDs following EFV exposure, with an anticipated surveillance of 95,000 births over four years (August 2014-August 2018).

Case 2:
Start date of dolutegravir is 6/1/2016 (ob card). Delivery date (b) (6) at 39 weeks GA and died shortly after birth. Estimated date of conception (b) (6). Description of abonormality noted abnormality in the head and skull exam described as anencephaly. No medical history (including no diabetes or use of insulin). No history of
seizures and no use of anti-epileptic (including sodium valproate) or other medication at conception. No diagnoses or other medications given in pregnancy.
Patient taking FeFol (iron + folate) starting (b) (6) (3rd month of pregnancy).
Unknown if there was a family history of neural tube defects.

Follow up information received on 14 May 2018:
The mother had a maternal age of 30 years. She had two pregnancies with one over 20 weeks gestation.
Mother's first weight in pregnancy was 66.5 kg on 11 April 2017.

Follow up information received via the Antiretroviral Pregnancy Registry on 23 May 2018:
The mother's LMP was provided (b) (6)
Additional information provided by the APR Birth Defect Evaluator:
ANENCEPHALY IS A TYPE OF NEURAL TUBE DEFECT IN WHICH THE ANTERIOR NEUROPORE DOES NOT CLOSE AT ABOUT 28 DAYS POST CONCEPTION.

Follow up information received on 25 July 2018:
The author reported that 'among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect) and anencephaly. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception.

The author concluded that 'we found a potential early signal for an increased prevalence of neural-tube
defects in association with dolutegravir-based antiretroviral therapy from the time of conception.
Our study is ongoing and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.'

Case ID: 14882044

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	IRON + FOLATE		Transplacental	UNK		11-Apr-2017		188 DAY

Reporter Source:

Study Report?: No **Sender Organization:** VIIV **503B Compounding Outsourcing Facility?:**

Case ID: 14882044

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882047

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BWA **Event Date:** 19-Oct-2017 **Outcomes:** CA,DE,OT, **Application Type:** NDA

FDA Rcvd Date: 02-Aug-2018 **Mfr Rcvd Date:** 25-Jul-2018 **Mfr Control #:** US-VIIV HEALTHCARE LIMITED-BW2018GSK083124 **Application #:** 204790

Patient Information:

Age: < 1 DAY **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Dolutegravir			Transplacental	UNK		29-Jun-2016	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Dolutegravir	477 Day	NA	NA				VIIV	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Foetal death	NA
Foetal exposure during pregnancy	NA
Iniencephaly	NA

Event/Problem Narrative:

This retrospective pregnancy case described the occurrence of iniencephaly in a 39-week-old infant. The mother was a subject enrolled in an open label study titled Dolutegravir Non-GSK study. The subject received dolutegravir from 29th June 2016.

The mother's last menstrual period was on (b) (6) and estimated date of delivery was (b) (6). The infant was exposed to dolutegravir during the first, second and third trimesters of pregnancy.

The infant was diagnosed with iniencephaly. Serious criteria included death, GSK medically significant and congenital anomaly. Additional event(s) included fetus macerated (serious criteria death and GSK medically significant) and drug exposure in utero. The outcome of iniencephaly was fatal on (b) (6). The outcome(s) of the additional event(s) included fetus macerated (fatal on (b) (6)). The infant died on (b) (6). The reported cause of death was foetus macerated and iniencephaly.

Case ID: 14882047

It was unknown if the investigator considered the iniencephaly and fetus macerated to be related to dolutegravir.

Additional information:
The Tsepamo study (R01HD080471) is an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and (2) to determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. The study is powered to detect at least a 2-fold increase in the risk of NTDs following EFV exposure, with an anticipated surveillance of 95,000 births over four years (August 2014-August 2018).

Case 4:
Start date of dolutegravir is 6/29/2016 (ob card). LMP (b) (6), delivery date (b) (6) at 39 weeks, stillbirth (macerated).
No medical history (including no diabetes or use of insulin). No history of seizures and no use of anti-epileptic (including sodium valproate) or other medication at conception. No diagnoses or other medications given in pregnancy.
Unknown if there was a family history of neural tube defects.

Follow up information received on 14 May 2018:
The mother had a maternal age of 31 years. She had two pregnancies of which one was past 20 weeks gestation.

Mother's first weight in pregnancy was 95.2 kg on 24 May 2017.

Follow up information received on 25 July 2018:
The author reported that 'among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect) and anencephaly. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception.

The author concluded that 'we found a potential early signal for an increased prevalence of neural-tube defects in association with dolutegravir-based antiretroviral therapy from the time of conception.
Our study is ongoing, and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.'

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882047

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: VIIV

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882048

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BWA **Event Date:** 12-Jan-2018 **Outcomes:** CA,DE,OT, **Application Type:** NDA

FDA Rcvd Date: 02-Aug-2018 **Mfr Rcvd Date:** 25-Jul-2018 **Mfr Control #:** US-VIIV HEALTHCARE LIMITED-BW2018GSK083116 **Application #:** 204790

Patient Information:

Age: < 1 DAY **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Dolutegravir			Transplacental	UNK		01-Aug-2016	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Dolutegravir	529 Day	NA	NA				VIIV	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Foetal exposure during pregnancy	NA
Spina bifida	NA

Event/Problem Narrative:

This retrospective pregnancy case described the occurrence of spina bifida, without mention of hydrocephalus, lumbar region in a 38-week-old infant. The mother was a subject enrolled in an open label study titled Dolutegravir Non-GSK study. The subject received dolutegravir from 1st August 2016.

Concomitant product exposures included vitamins nos (Multivitamin).

The mother's last menstrual period was on (b) (6) and estimated date of delivery was (b) (6). The infant was exposed to dolutegravir during the first, second and third trimesters of pregnancy.

The infant was diagnosed with spina bifida, without mention of hydrocephalus, lumbar region. Serious criteria included death, GSK medically significant, clinically significant/intervention required and congenital anomaly. Additional event(s) included drug exposure in utero. The outcome of spina bifida, without mention of hydrocephalus, lumbar region was fatal on (b) (6). The infant died on (b) (6)

Case ID: 14882048

(b) (6). The reported cause of death was spina bifida, without mention of hydrocephalus, lumbar region.

It was unknown if the investigator considered the spina bifida, without mention of hydrocephalus, lumbar region to be related to dolutegravir.

Additional information:
The Tsepamo study (R01HD080471) is an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and (2) to determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. The study is powered to detect at least a 2-fold increase in the risk of NTDs following EFV exposure, with an anticipated surveillance of 95,000 births over four years (August 2014-August 2018).

Case 3:
Start date of dolutegravir is 8/1/2016 (ob card). LMP (b) (6), delivery date (b) (6) at 38 weeks. Died 4 days after birth.
No medical history (including no diabetes or use of insulin). No history of seizures and no use of anti-epileptic (including sodium valproate) or other medication at conception. No diagnoses or other medications given in pregnancy.
Patient taking a multivitamin starting (b) (6) (6th month of pregnancy).
Unknown if there was a family history of neural tube defects.

Follow up information received 04 May 2018:
The mother had a maternal age of 35 years. She had five pregnancies of which four were over 20 weeks gestation.

Mother's first weight in pregnancy was 52 kg on 15 November 2017.

Follow up information received on 25 July 2018:
The author reported that 'among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect) and anencephaly. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception.

The author concluded that 'we found a potential early signal for an increased prevalence of neural-tube defects in association with dolutegravir-based antiretroviral therapy from the time of conception.
Our study is ongoing, and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.'

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882048

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	MULTIVITAMIN		Transplacental	UNK		14-Dec-2017		29 DAY

Reporter Source:

Study Report?: No **Sender Organization:** VIIV **503B Compounding Outsourcing Facility?:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882049

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BWA **Event Date:** 16-Apr-2018 **Outcomes:** CA,OT, **Application Type:** NDA

FDA Rcvd Date: 02-Aug-2018 **Mfr Rcvd Date:** 25-Jul-2018 **Mfr Control #:** US-VIIV HEALTHCARE LIMITED-BW2018GSK083007 **Application #:** 204790

Patient Information:

Age: 1 YR **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Dolutegravir			Transplacental	UNK		20-Jun-2016	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Dolutegravir	665 Day	NA	NA				VIIV	

Event Information:

Preferred Term (MedDRA Version: 21.0)	ReC
Encephalocele	NA
Foetal exposure during pregnancy	NA

Event/Problem Narrative:

This retrospective pregnancy case described the occurrence of encephalocele in a 33-week-old infant. The mother was a subject enrolled in an open label study titled Dolutegravir Non-GSK study. The subject received dolutegravir from 20th June 2016.

The parent's medical history included gestational hypertension.

Concomitant product exposures included methyldopa.

The mother's last menstrual period was on (b) (6) and estimated date of delivery was (b) (6). The infant was exposed to dolutegravir during the first, second and third trimesters of pregnancy.

The infant was diagnosed with encephalocele. Serious criteria included GSK medically significant, clinically significant/intervention required and congenital anomaly. Additional event(s) included drug exposure in utero. The outcome of encephalocele was unknown.

Case ID: 14882049

It was unknown if the investigator considered the encephalocele to be related to dolutegravir.

Additional information:
The Tsepamo study (R01HD080471) is an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and (2) to determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. The study is powered to detect at least a 2-fold increase in the risk of NTDs following EFV exposure, with an anticipated surveillance of 95,000 births over four years (August 2014-August 2018).

Case 1:
Start date of dolutegravir 6/20/2016 (mother's report and OB card). This was her initial regimen, no change to ART during pregnancy. Mother's reported LMP was (b) (6) Delivery date (b) (6), gestational age recorded as unknown but 33 weeks from LMP (and almost two years after DTG initiation).
Infant was discharged alive.
No medical history (including no diabetes or use of insulin). No history of seizures and no use of anti-epileptic (including sodium valproate) or other medication at conception. Developed gestational hypertension and started Methyldopa on 1/31/2018, no other medications started in pregnancy. Not taking folate or multivitamin during pregnancy. Unknown if there was a family history of neural tube defects.

Follow up information received on 14 May 2018:
The mother had a maternal age of 30 years. Three pregnancies with two reaching more than 20 weeks gestation. Start date of dolutegravir confirmed as 20 June 2016.

Mother's first weight in pregnancy was 78 kg on 16 November 2017.

Follow up information received on 25 July 2018:
The author reported that 'among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect) and anencephaly. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception.

The author concluded that 'we found a potential early signal for an increased prevalence of neural-tube
defects in association with dolutegravir-based antiretroviral therapy from the time of conception.
Our study is ongoing, and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.'

FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 14882049

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	METHYLDOPA		Transplacental	UNK		31-Jan-2018	16-Apr-2018	75 DAY

Reporter Source:

Study Report?: No **Sender Organization:** VIIV **503B Compounding Outsourcing Facility?:**

Literature Text: