

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PID#: D050365

DATE: August 24, 2006

TO: Lisa L. Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Joslyn Swann, Pharm.D., M.G.A.,
Post-marketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

SUBJECT: 1-year Post-Pediatric Exclusivity Post-marketing Adverse Event Review
Drug: Novolog® (insulin aspart recombinant)
NDA: 020-986
Pediatric Exclusivity Approval Date: May 24, 2005

1.0 Executive Summary

The Adverse Event Reporting System (AERS) database was searched for reports of adverse events (serious and non-serious) occurring with the use of Novolog® in pediatric patients. Up to the "data lock" date of June 24, 2006, AERS contained 1338 reports for Novolog® (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 11.5% of the total (154/1338).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, May 24, 2005 to May 24, 2006. We used an AERS data lock date of June 24, 2006, to allow time for reports received up to May 24, 2006, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 284 reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately

9.9% of the total number of reports (28/284). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

Within the 1-year pediatric exclusivity period, 26 pediatric cases were identified with the following distribution of events: 19 with labeled events, 4 with unlabeled events that occurred during exposure via maternal use, and 3 deaths. In addition, 1 death occurred outside of the exclusivity period, and is described in section 4.2.1.

When collectively reviewing the *in utero* exposure cases, one might speculate about an association between Novolog® exposure and congenital anomalies. A search of the current medical journals via PubMed did not identify articles associating recombinant insulins like insulin aspart and congenital anomalies. And the effect of the mothers' diabetic condition in the occurrence of the congenital anomalies can not be ruled out. Galindo et al stated studies have showed a 3- to 5-fold increase in the major malformation rate in women with poor metabolic control (early maternal HbA_{1c} concentration >7%).^{5,6} But no specific pattern was detected with the anomalies in this series.

Although, a point of interest to explore may be to discern if there is increasing use of recombinant insulin products in females of child-bearing age, given the obesity rise in this country and associated Type 2 diabetes. DDRE will defer to the Pregnancy team and OPT as to whether a further exploration of recombinant insulins and congenital malformations is warranted at this time (i.e. a review of other recombinant insulins and congenital anomalies in AERS or other databases).

As for the labeled events (n=19), the reported adverse events represent a profile similar to that of the adult population. Review of these cases showed adverse events (diabetic ketoacidosis, convulsions, and hypoglycemia)⁴ that were similar to those identified by the Medical Officer in his clinical review of the supplemental New Drug Application (NDA) for use in children and adolescents ages 2-18 years with Type 1 diabetes. No new trends of adverse events were identified in this case series and no label changes are recommended. Therefore, DDRE will continue routine postmarketing surveillance of all reports submitted to AERS for Novolog®.

TABLE OF CONTENTS

2.0 Products, Indications, Pediatric Labeling, and Pediatric Filing History	3
2.1 Products	3
2.2 Indications	3
2.3 Pediatric Labeling.....	3
2.4 Pediatric Filing History	5
3.0 AERS Search Results: Insulin Aspart.....	6
3.1 Table 1: Count of All Reports – from marketing approval	6
3.2 Table 2: Count of All Reports – from pediatric exclusivity approval date	7
4.0 Post-marketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity	8
4.1 Case Characteristics	8

4.2 Summary of Cases.....	9
4.2.1 Fatal Cases	9
4.2.2 Non-Fatal Cases.....	11
4.2.2.1 Unlabeled/Unexpected Cases.....	11
4.2.2.2 Labeled/Expected Cases.....	11
5.0 Conclusion	14
Appendix 1.....	15

2.0 Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Products:¹

Drug Name / FDA Application Number	Approval Date	Dosage Form / Route	Strength	Marketing Status	Company
Novolog® / NDA # 020986	June 7, 2000	Injectable / subcutaneous	100 units/ml	Prescription	Novo Nordisk Inc

2.2 Indications:²

Novolog is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia. Because Novolog has a more rapid onset and a shorter duration of activity than human regular insulin, Novolog given by injection should normally be used in regimens with an intermediate or long-acting insulin. Novolog may also be infused subcutaneously by external insulin pumps. Novolog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (See WARNINGS, PRECAUTIONS [especially Usage in Pumps], Information for Patients [especially For Patients Using Pumps], Mixing of Insulins, DOSAGE AND ADMINISTRATION, RECOMMENDED STORAGE.)

2.3 Pediatric Labeling:³

Pediatric use and effects are addressed in the following sections of the label:

a) CLINICAL PHARMACOLOGY, Special Populations:

Children and Adolescents –The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade \geq 2], n=9) with Type 1 diabetes. The relative differences in pharmacokinetics and

¹-U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Drugs@FDA. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=NOVOLOG>. Accessed: July 2006.

² NovoLog®. Prescribing Information. Available at: <http://www.novolog.com>. Accessed: July 2006.

³ NovoLog®, Insulin aspart (rDNA origin) injection. Prescribing Information. Available at: www.novolog.com. Accessed: July 2006.

pharmacodynamics in children and adolescents with Type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with Type 1 diabetes.

b) PRECAUTIONS, Carcinogenicity, Mutagenicity, Impairment of Fertility:

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

c) PRECAUTIONS, Pregnancy--Teratogenic Effects--Pregnancy Category C:

There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant women. NovoLog should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Subcutaneous reproduction and teratology studies have been performed with NovoLog and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the

human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

d) PRECAUTIONS, Nursing Mothers:

It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

e) PRECAUTIONS, Pediatric Use:

A 24-week, parallel-group study of children and adolescents with Type 1 diabetes (n=283) age 6 to 18 years compared the following treatment regimens: NovoLog (n=187) or Novolin R (n=96). NPH insulin was administered as the basal insulin. NovoLog achieved glycemic control comparable to Novolin R, as measured by change in HbA_{1C}. The incidence of hypoglycemia was similar for both treatment groups. NovoLog and regular human insulin have also been compared in children with Type 1 diabetes (n=26) age 2 to 6 years. As measured by end-of-treatment HbA_{1C} and fructosamine, glycemic control with NovoLog was comparable to that obtained with regular human insulin. As observed in the 6 to 18 year old pediatric population, the rates of hypoglycemia were similar in both treatment groups.

2.4 Pediatric Filing History:

A Written Request (WR) for a pediatric study was issued on December 14, 1999. Several WR amendments were issued, and the dates of issuance are as follows: July 20, 2001, July 2, 2002, April 15, 2003, December 17, 2003, May 7, 2004, and October 5, 2004. Novo Nordisk Pharmaceuticals, Inc (sponsor) submitted supplemental NDA number S-033 on March 14, 2005 in accordance with WR amendment No 6.⁴

The Pediatric Exclusivity Board met on May 24, 2005 and granted Pediatric Exclusivity to the sponsor based on this submission. The supplement provided for the use of insulin aspart for treatment of Type 1 diabetes in children and adolescents ages 2 through 18 years.⁴ The pediatric efficacy supplement was approved on September 13, 2005.⁴

⁴ Gabry EK. Clinical Review of NDA 20986-S33. Completed August 23, 2005 Available in the Division Files System. Accessed: July 2006.

3.0 AERS Search Results: Insulin Aspart

3.1 Table 1: Crude Counts of AERS Reports, searches including all sources, U.S. & foreign from marketing approval date (June 7, 2000) through AERS cut-off date (June 24, 2006)

Table 1: Crude Counts¹ of AERS Reports for Insulin Aspart from All Sources from Marketing Approval Date (June 7, 2000) through AERS cut-off date (June 24, 2006) <i>(US counts in parentheses)</i>			
	All reports (US)	Serious² (US)	Death (US)
Adults (≥ 17 yrs.)	1051 (828)	491 (275)	30 (8)
Pediatrics (0-16 yrs.)	154 (117)	72 (35)	5 (0)
Age unknown (Null values)	133 (111)	53 (31)	1 (0)
Total	1338 (1056)	616 (341)	36 (8)

¹ May include duplicates

² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

Figure 1: Reporting trend for all reports (N=1338) from approval: June 7, 2000 through AERS cut-off date (June 24, 2006)

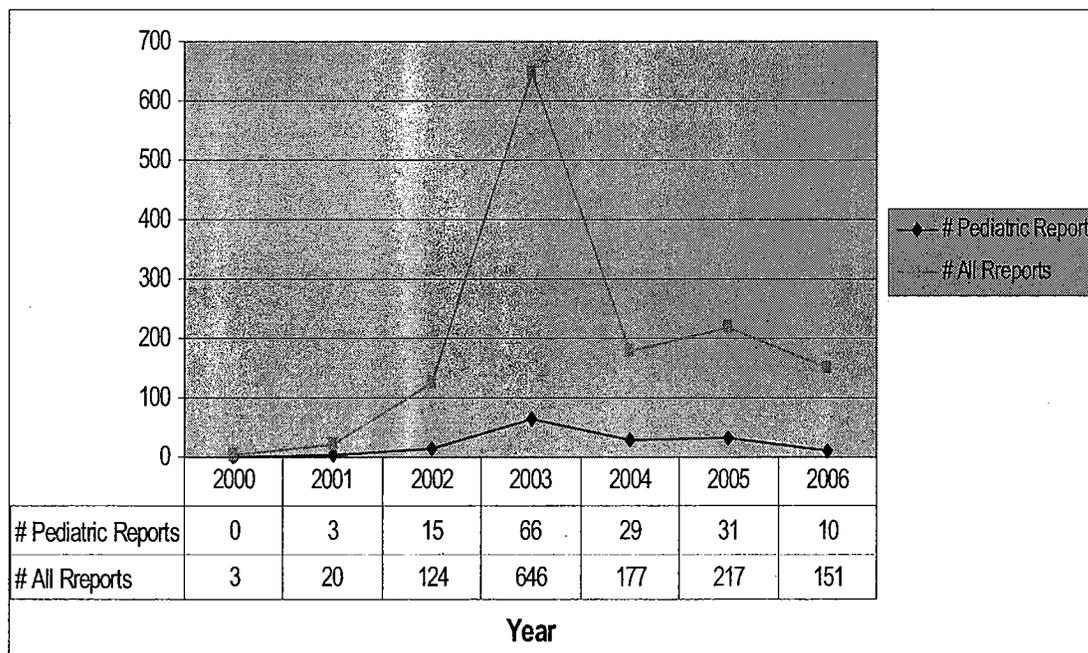
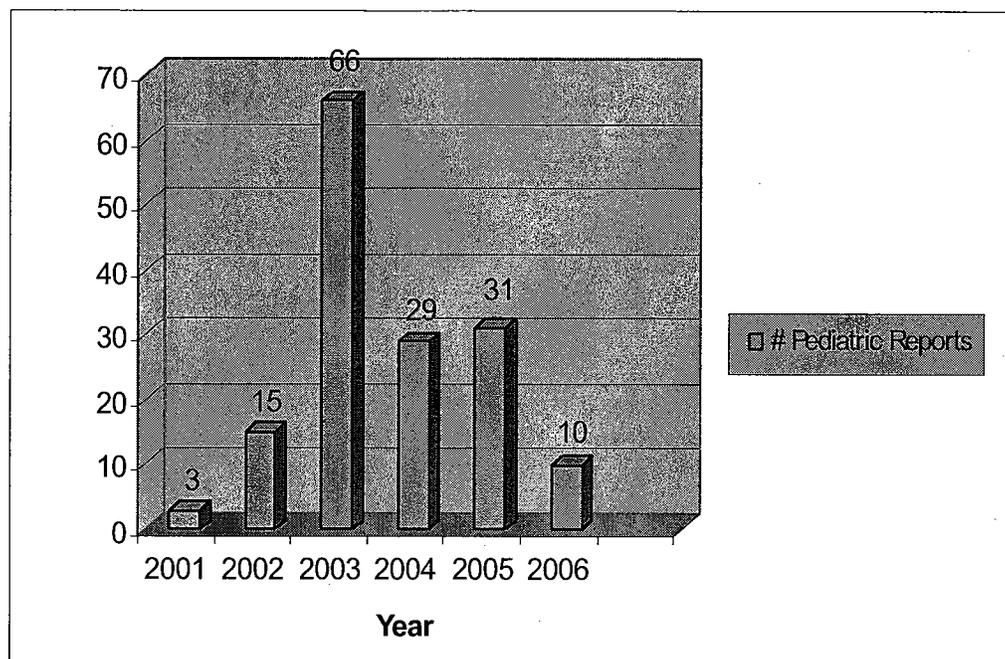


Figure 2: Reporting trend for all pediatric reports (N=154) from approval: June 7, 2000 through AERS cut-off date (June 24, 2006)



3.2 Table 2: Crude Counts of AERS reports, searches including all sources, U.S. & foreign from pediatric exclusivity approval date (May 24, 2005) through AERS cut-off date (June 24, 2006) (pediatric exclusivity period)

	All reports (US)	Serious² (US)	Death (US)
Adults (≥ 17 yrs.)	230 (135)	202 (108)	12 (1)
Pediatrics (0-16 yrs)	28 (18)	24 (14)	3 (0)
Age unknown (Null Values)	26 (16)	23 (13)	0 (0)
Total	284 (169)	249 (135)	15 (1)

¹ May include duplicates

² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

4.0 Post-marketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

4.1 Case Characteristics:

Table 3: Characteristics of Pediatric Cases reported during the pediatric exclusivity approval through AERS cut-off date (May 24, 2005 through June 24, 2006) N=26	
<u>Gender</u>	n=25
Female	11
Male	14
<u>Age at time of event</u>	
0 < 1 month	6
1 month < 2 yrs	2
2-5 yrs	3
6-11 yrs	6
12-16 yrs	9
Mean	7.3 yrs
Median	8.0 yrs
Range	4 days-15 yrs
<u>Origin</u>	
US	17
Foreign	9
<u>Event date</u>	n=25
2003	2
2004	6
2005	16
2006	1
<u>Time to Event, (days)</u>	n=11
Mean	264
Median	122
Range	1-1214
<u>Indications</u>	
Type 1 diabetes mellitus	20
Exposure via Maternal Use	6
<u>Outcomes[†]</u>	
Congenital Anomaly	3
Death	3
Disability	1
Hospitalization	14
Life-Threatening	5
Other	9
Required intervention	5

[†] Outcomes are not mutually exclusive; one case could contain more than one outcome.

4.2 Summary of Cases during the one-year post-pediatric exclusivity period

AERS was searched for pediatric cases associated with insulin aspart therapy. Our search resulted in 28 reports. After removing 2 duplicate reports, 26 cases remained.

Within the 26 cases, 14 (53.8%) resulted in a hospitalization or emergency room visit, and 3 fatal cases were reported. Of the 3 fatal cases, one infant expired four days after birth from delivery complications including brain damage; one 4-months-old infant died from complications resulting from truncus arteriosus communis (a major malformation); and one 14-year-old adolescent died of an acute asthma attack. The average patient age was 7.3 years; ages ranged from 4 days to 15 years. Six cases reported intrauterine exposure from mothers who were treated with Novolog® during pregnancy. Patients' daily doses were variable due to individualized needs for glycemic control.

This case series (N=26) was stratified into fatal cases (section 4.2.1) and non-fatal cases (section 4.2.2) for further discussion. However, to identify all fatal pediatric cases for Novolog®, AERS was searched a second time utilizing dates from market approval (June 7, 2000) through May 24, 2005. This search identified 1 additional pediatric case, age less than 17 years (section 4.2.1 for ISR#4431222).

4.2.1 Fatal Case Narratives, n=4

ISR #: 4682908, Foreign (Major Congenital Malformation)

A pregnant female of unknown age, who had Type 1 diabetes mellitus, was initiated into an insulin aspart trial (trial ID: ANA-1474) on June 30, 2004. After a spontaneous rupture of her membrane, she gave birth to a female baby on _____. Shortly after birth, the neonate developed a slight heart murmur and had slight cyanosis of the hands only. She was given oxygen therapy. On _____ an ultrasound of the heart revealed a congenital heart malformation (truncus arteriosus communis). On _____ a cardiovascular reconstruction operation was performed successfully. On _____ another operation to improve the heart-lung circuit was performed. Despite corrective surgical interventions, the infant expired on _____, the exact cause of death was not reported. The mother's medical history during her pregnancy included: headaches, vaginal bleeding, candida vaginalis, common cold, vomiting, and heartburn. Her concomitant medications included NPH insulin, paracetamol, gravitamon (multivitamin and mineral supplement), clotrimazole, and a product containing aluminium glycinate magnesium oxide.

ISR #: 4748701, Foreign (Asthma-related)

A 14-year-old male, had been treated with insulin detemir and insulin aspart (dosing regimen not reported) since August 2004, for approximately 4-5 months for treatment of diabetes mellitus. On _____ the adolescent was found dead in bed. He had been well the night before his death. The patient had a medical history positive for asthma and arrhythmia. The report stated that "the post mortem suggests an acute asthma attack, even though the patient had not had an attack in 8 years." No additional information was provided.

ISR#: 4752151, Foreign (Hypoxic Encephalopathy)

A pregnant female (age not reported) was enrolled in a clinical trial for insulin aspart on November 8, 2003, for treatment of Type 1 diabetes mellitus (trial ID: ANA-1474). On _____, she was admitted to the labor ward fully dilated. Before delivery, the mother's concomitant medications included insulatard. No medical history for the mother was provided. She had been in labor for 5 hours and 59 minutes, and attempts to deliver her baby with forceps failed so an emergency caesarean section was performed. As a result of the obstructed delivery, the baby boy experienced brain damage (hypoxic ischemic encephalopathy) and fetal distress at birth. He was admitted to the neonatal intensive care unit and placed on a ventilator. Brow presentation and severe bruising to the neonate's head were noted. On May 17th, the neonate had continuous seizures throughout the day; the SaO2 monitor was down to 40 and the neonate experienced bradycardia. In addition, a cranial ultrasound confirmed that he suffered from severe hypoxic ischemic encephalopathy. The MRI scan performed on _____, concluded that the findings were consistent with acute ischemia affecting the thalami and the posterior part of the lentiform nuclei. On that same day, the neonate expired. No autopsy was performed at the parents' request.

Below is the additional case that was mentioned above and reported outside of the Pediatric Exclusivity period.

ISR#: 4431222, Foreign (Alcohol Overdose)

A 9-year-old male was initiated on insulin glargine (date and dosing regimen unknown) for Type 2 diabetes mellitus. Approximately six months after starting insulin glargine, the patient died. Relevant medical history and concomitant drugs were not reported. At autopsy, the cause of death was listed as a possible alcohol overdose. Post mortem results are pending.

In conclusion, we reviewed 4 fatal cases with various adverse events associated with Novolog® use or *in utero* exposure. In the two fatalities with *in utero* exposure, it is difficult to determine from a spontaneous reporting system such as AERS whether the events were due to exposure to Novolog® or are due to the mother's diabetic condition.^{5,6} Also, the impact of other maternal factors such as smoking, alcohol use, and concomitant medications can not be ruled out. While AERS data is better suited for signal detection of rare, serious, acute or life-threatening adverse events, AERS is not an optimal tool to assess latent events such as malignancies or congenital anomalies. In the case of the 14-year old and the 9-year old, their deaths appeared to be associated with alternate causes.

⁵ Wren C et al. Cardiovascular malformations in infants of diabetic mothers. *Heart*. 2003 Oct;89(10):1217-20.

⁶ Galindo A et al. Outcome of fetuses in women with pregestational diabetes mellitus. *J Perinat Med*. 2006;34(4):323-31.

4.2.2 Non-Fatal Cases

4.2.2.1 Unlabeled/Unexpected Cases

Of the 23 non-fatal cases, 4 cases had *in utero* exposure (see summaries below). The unlabeled events are underlined.

4.2.2.1.1 *In utero* exposure events (n=4)

One case (ISR#4682919) reported a fetus in the first trimester exposed to insulin lispro, and regular insulin in addition to Novolog®. Following delivery, the newborn experienced neonatal hypoglycemia and a congenital anomaly (ankyloglossia). The ankyloglossia was considered “slight” and was reported to have “stabilized” approximately six weeks after birth.

One case (ISR#4678599) reported a fetus in the first trimester exposed to multiple drugs including Novolog®. The neonate was born prematurely by natural delivery in gestational week 37, and experienced urinary retention, neonatal asphyxia, and a hypoxic-ischemic lesion of the central nervous system.

One case (ISR#4733297) reported *in utero* exposure to Novolog®. On _____ the newborn was diagnosed with neonatal meningomyelocele. The diagnosis was later changed as the infant underwent a computed tomography scan which showed dysmorphism of the right frontal lobe, increased frontal subarachnoid space, and asymmetry of the lateral ventricle on May 12, 2005.

One case (ISR#4749464) reported a newborn exposed *in utero* to Novolog® during maternal use. Or _____ neonate was delivered prematurely, at gestational week 32 and 2 day, by an emergency caesarean section, and experienced neonatal hypoglycemia. The baby’s blood glucose was 24 mg/dL and she received was treated with 5% glucose infusion. The neonate was reported to have recovered on same day.

4.2.2.2 Labeled/Expected Cases

Of the 23 non-fatal cases, 19 cases reported various events that are either listed or implied in the current product labeling for Novolog®; the identified events were similar to those observed in the adult population. These events, the numbers of occurrences in the case series, and their reference in the product labeling are listed below in Table 4. Characteristics of the patients associated with the labeled events are below in Table 5.

Table 4: Count of *Labeled Adverse Events* for All Pediatric Cases from date Pediatric Exclusivity was Granted (May 24, 2005) through AERS cut-off date (June 24, 2006)

Adverse Event	Label Reference	Number of Events [†]
Hyperglycemia	AR; P; W	11
Hypoglycemia	AR; C; O; P; W	6
Ketosis	AR; P; W	5
Seizure	O	4
Anaphylactic Reaction	AR; P	1
Lipoatrophy	AR	1
Loss of Consciousness	P	1

[†] Events are not mutually exclusive; one case could contain more than one event.

Legend: ADVERSE REACTION (AR); CONTRAINDICATIONS (C); OVERDOSAGE (O); PRECAUTIONS (P); WARNINGS (W)

Table 5: Characteristics of Pediatric Cases with *Labeled Adverse Events* reported during the Pediatric Exclusivity approval through AERS cut-off date (May 24, 2005 through June 24, 2006)

N=19

<u>Gender</u>	n=18
Female	7
Male	11
<u>Age at time of event</u>	
0 < 1 month	0
1 month < 2 yrs	2
2-5 yrs	3
6-11 yrs	6
12-16 yrs	8
Mean	9.2 yrs
Median	9.0 yrs
Range	13 months -15 yrs
<u>Origin</u>	
US	17
Foreign	2
<u>Event date</u>	n=18
2003	2
2004	3
2005	12
2006	1

Table 5 continued:

Table 5: Characteristics of Pediatric Cases with Labeled Adverse Events reported during the Pediatric Exclusivity approval through AERS cut-off date (May 24, 2005 through June 24, 2006)	
N=19	
Time to Event, (days)	n=10
Mean	259
Median	111
Range	1-1214
Outcomes[†]	
Hospitalization	12
Life-Threatening	4
Other	5
Required intervention	5

[†] Outcomes are not mutually exclusive; one case could contain more than one outcome.

In addition to the labeled adverse events above, 2 cases of medication errors were identified (ISR#s 4680597; 4842053). In both cases, the drugs involved in the administration error were Novolog® and Novolog® Mix (a dual-acting insulin aspart), and both patients required visits to the emergency room.

On July 24, 2006, the Division of Medication Errors and Technical Support (DMETS), OSE, was contacted regarding medication errors from products with similar names. Scott Dallas, Safety Evaluator in DMETS, stated that a number of consults have been completed regarding these two products including a consult evaluating the implementation of the International Diabetes Federation color coding for insulin products (completed in May 2004).⁷ In addition, he stated that DMETS will continue to monitor the two products.

ISR#: 4680597, Domestic

A 14-year-old boy who given Novolog® Mix, from March 22, 2005 to April 29, 2005, instead of his prescribed Novolog® for use in his insulin pump for Type 1 diabetes mellitus. The medication error occurred on March 22, 2005, and on April 8, 2005, he was taken to the emergency room after he began having seizures at home. His blood glucose was 56 mg/dL and was treated with glucagon, improved, and was released. He continued to have intermittent seizures due to low blood glucose, which were treated with glucagon. On April 29, 2005, his mother realized the medication error and notified the pharmacy. At the time of the report, the event had resolved.

⁷ Hoppes C. Labeling Review for Novolog® and Novolog® Mix 70/30, N020-986 and N021-172. Completed May 19, 2004. Available in Division Files System.

ISR #: 4842053, Domestic

A 14-year-old boy experienced increased blood glucose and vomiting after receiving Novolog® instead of his prescribed Novolog® Mix for treatment of Type 1 diabetes. The patient experienced several days of high blood sugars, which resulted in an emergency room visit. In the emergency room, the physician discovered the pharmacy error. The patient was treated with 54 units of Novolog® Mix and released. The event resolved.

5.0 Conclusion

When collectively reviewing the *in utero* exposure cases, one might speculate about an association between Novolog® exposure and congenital anomalies. While the PRECAUTIONS section of the product label cites “visceral/skeletal abnormalities in rats”, no reference is made about human exposure. A search of the current medical journals via PubMed did not identify articles associating recombinant insulins like insulin aspart to congenital anomalies. And the effect of the mothers’ diabetic condition in the occurrence of the congenital malformations can not be ruled out. Galindo et al stated that there was a positive correlation between increased maternal hemoglobin A_{1C} (HbA_{1C}) levels and the observed rate of fetal malformations. Studies have shown a 3- to 5-fold increase in the major malformation rate in women with poor metabolic control (early maternal HbA_{1C} concentration >7%).^{5,6} But no specific pattern was detected with the anomalies in this series.

Although, a point of interest to explore may be to discern if there is increasing use of recombinant insulin products in females of child-bearing age, given the obesity rise in this country and associated Type 2 diabetes. DDRE will defer to the Pregnancy team and OPT as to whether a further exploration of recombinant insulins and congenital malformations is warranted at this time (i.e. a review of other recombinant insulins and congenital anomalies in AERS or other databases).

As for labeled events (n=19), the reported adverse events represent a profile similar to the adult population. Review of these cases showed adverse events (diabetic ketoacidosis, convulsions, and hypoglycemia)⁴ that were similar to those identified by the Medical Officer in his clinical review of the supplemental NDA for use in children and adolescents ages 2-18 years with Type 1 diabetes.⁴ No new trends of adverse events were identified in this case series and no label changes are recommended. Therefore, DDRE will continue routine postmarketing surveillance of all reports submitted to AERS for Novolog®.

Joslyn Swann, Pharm.D.
Safety Evaluator

Concur:

Lanh Green, Pharm.D., M.P.H.
Team Leader

Appendix 1

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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

/s/

Joslyn Swann
8/24/2006 04:50:03 PM
DRUG SAFETY OFFICE REVIEWER

Lanh Green
8/25/2006 10:05:53 AM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
8/25/2006 10:31:53 AM
MEDICAL OFFICER