CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209379Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 24, 2019
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209379
Product Name and Strength:	Selenious Acid Injection, USP 600 mcg*/10 mL (60 mcg*/mL) of selenium
Applicant/Sponsor Name:	American Regent, Inc.
FDA Received Date:	April 10, 2019 April 23, 2019
OSE RCM #:	2018-2364-2
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container label and carton labeling (Appendix A) and prescribing information (PI) to determine if it is acceptable from a medication error perspective. The revision is in response to recommendation that we made during a previous label and labeling review.[1]

2 CONCLUSION

We find the revised PI, container label, and carton labeling acceptable from a medication error perspective. We have no further recommendations at this time.

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[1]Abraham, S. Label and Labeling Review for Selenious Acid Injection (NDA 209379). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 20. RCM No.: 2018-2364-1

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04/24/2019 02:53:16 PM

SARAH K VEE
04/24/2019 03:55:39 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 16, 2019

To: Thao Vu, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for SELENIOUS ACID INJECTION, for intravenous use

NDA: 209379

In response to DGIEP's consult request dated November 7, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Selenious Acid Injection.

PI: OPDP has no comments on the proposed labeling at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor and received by OPDP via email on April 11, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 20, 2019
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209379
Product Name and Strength:	Selenious Acid Injection, USP 600 mcg*/10 mL (60 mcg*/mL) of selenium
Applicant/Sponsor Name:	American Regent, Inc.
FDA Received Date:	March 12, 2019
OSE RCM #:	2018-2364-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

[1]Abraham, S. Label and Labeling Review for Selenious Acid Injection (NDA 209379). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 05. RCM No.: 2018-2364

The revised container label and carton labeling are unacceptable from a medication error perspective. The Applicant has not followed the recommended format for the expiration date. The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.

3 RECOMMENDATIONS FOR AMERICAN REGENT, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling:

1. As currently displayed, the expiration date is presented with three letter alphabetical characters for the month and two digits for theyear (MAR19). The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors. We recommend the expiration date to be in the format of "YYYY-MMM" if alphabetical characters are used to represent the month and a hyphen or a space should be used to separate the portions of the expiration date (e.g., 2019-MAR).

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SARAH K VEE
03/20/2019 01:04:44 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 5, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 209379
Product Name and Strength:	Selenious Acid Injection, USP 600 mcg*/10 mL (60 mcg*/mL) of selenium
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	American Regent, Inc.
FDA Received Dates:	October 30, 2018 February 25, 2019
OSE RCM #:	2018-2364
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.
DMEPA Associate Director:	Mishale Mistry, Pharm.D., MPH

1 REASON FOR REVIEW

As part of the approval process for Selenious Acid Injection, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Selenious Acid Injection prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 FINDINGS AND RECOMMENDATIONS

The applicant proposes to introduce a product with the established name, selenious acid injection, and strength of 600 mcg/10 mL (60 mcg/mL) based on the active moiety selenium. There is an unapproved product currently available with the established name of *selenium injection* and strength of 400 mcg/10 mL (40 mcg/mL), based on the active moiety selenium. Per the USP monograph, the established name for this product is selenious acid injection and the strength should be labeled by the amount of selenium. In the applicant's proposal, unapproved product and the USP monograph, there is in an inconsistency between the established name (selenious acid) and strength (based on selenium).

Due to familiarity with the unapproved product, in order to reduce healthcare provider confusion and mitigate the risk of dosing errors, DMEPA recommends that the expression of the strength for the proposed product is consistent with how the strength is expressed for the unapproved product (based on the active moiety selenium). However, DMEPA also recognizes that there may be a concern of healthcare provider unfamiliarity with 'selenious acid' (established name of proposed product) and 'selenium' (established name of unapproved product).

On February 22, 2019, we discussed the issue of strength expression and established name with DGIEP and Office of Pharmaceutical Quality (OPQ). Per our discussion, we agreed upon the established name as 'selenious acid' per the USP monograph and expressing the strength as the active moiety (selenium), 600 mcg/10 mL (60 mcg/mL). However, to provide additional clarity on the relationship between selenious acid and selenium, an additional clarifying statement will be added on the labels and labeling. The following format will be displayed on the container label and carton labeling:

Selenious Acid Injection, USP
600 mcg*/10 mL
(60 mcg*/mL)
of selenium

Side panel:
*Each mL provides 60 mcg of selenium (present as 98 mcg of selenious acid)

The following statement will be included in Section 3 Dosage Forms and Strengths of the Prescribing Information:

Injection: 600 mcg/10 mL (60 mcg/mL) of selenium. (b) (4)

Table 2 below includes the identified medication error issues with the submitted container label and carton labeling, our rationale for concern, and the proposed recommendations to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The established name (selenious acid) and the strength expression (based on selenium) is not consistent.	We are concerned that the mismatch in the established name and strength may lead to confusion among healthcare providers.	Revise the strength presentation as follows: 600 mcg*/10 mL (60 mcg*/mL) of selenium <u>Side panel:</u> *Each mL provides 60 mcg of selenium (present as 98 mcg of selenious acid)
2.	The net quantity statement is more prominent than the	From post-marketing experience, the risk of numerical confusion	Decrease the prominence and relocate the net quantity statement away from the

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	product strength statement and is located in close proximity to the product strength statement.	between the strength and net quantity increases when the net quantity statement is more prominent and located in close proximity to the strength statement.	product strength, such as to the bottom of the principal display panel.
3.	The format for expiration date is not defined.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	Negative statement (b) (4)	Due to our understanding of post-marketing reports, negative statements may have the opposite of intended meaning because the word 'not' can be	Remove the negative statement ' (b) (4)

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		overlooked and the warning be misinterpreted as an affirmative action.[a]	
5.	The dilution and admixing statement is absent.	We recommend adding a statement to inform healthcare providers that this product must be diluted and used as an admixture in parenteral nutrition solutions to minimize the risk of administering the drug as an intravenous bolus.	Revise the route of administration statement (*For intravenous use*) to read: "For intravenous use after dilution and admixing".
Container Label			
1.	The usual dose statement is absent on the container label.	As per 21 CFR 201.55, the usual dose statement is required on the container label.	Add the usual dose statement, "Usual dose: See recommended dose in the prescribing information" on the container label.
Carton Labeling			
1.	The product identifier required under the Drug Supply Chain Security Act (DSCSA)[b] is missing.	DSCSA requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[a] Institute for Safe medication practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

[b]The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 2. Identified Issues and Recommendations for American Regent, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		November 27, 2018, respectively.	
2.	The usual dose statement refers to PI as (b) (4)	As per 21 CFR 201.55, the usual dose statement is required on the carton labeling.	Revise the usual dose statement to read "Usual dose: See recommended dose in the prescribing information" on the carton labeling.

4 CONCLUSION

We defer to OPQ to provide revisions to Section 3 Dosage Forms and Strengths in the prescribing information, as discussed above in Section 3. We have no additional recommendations for the PI at this time.

Our evaluation of the proposed Selenious Acid Injection container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided Table 2 for the Applicant. We ask that the Division convey Table 2 *in its entirety* to American Regent, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Selenious Acid Injection that American Regent, Inc. submitted on October 30, 2018.

Table 3. Relevant Product Information for Selenious Acid Injection	
Initial Approval Date	N/A
Active Ingredient	selenious acid
Indication	Selenious Acid Injection is indicated in pediatric patients and adults as a source of selenium for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Route of Administration	intravenous
Dosage Form	injection
Strength	600 mcg*/10 mL (60 mcg*/mL) of selenium
Dose and Frequency	Adults: 60 (b) (4) mcg/day Pediatric Patients ≥ (b) (4)
How Supplied	Carton of 25 vials 60 mcg/mL of selenium present as 98 mcg/mL selenious acid (clear and colorless solution) in a 10 mL Pharmacy Bulk Package Vial
Storage	Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Selenious Acid Injection labels and labeling submitted by American Regent, Inc.

- Container label received on February 25, 2019
- Carton labeling received on February 25, 2019
- Prescribing information (not imaged) received on October 30, 2018

F.2 Label and Labeling Images

Container label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: February 4, 2019 **Date consulted:** November 7, 2018

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Selenious acid injection

NDA: 209379

Applicant: Luitpold Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) formatting recommendations

Proposed Indication: as a source of selenium for parenteral nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated

Materials Reviewed:

- October 12, 2018, submission for NDA 209379 for selenious acid injection
- October 31, 2018, submission of labeling for NDA 209379

Consult Question: "Assistance in review of proposed NDA labeling and PLLR (Pregnancy and Lactation Labeling Rule) labels"

INTRODUCTION AND BACKGROUND

On October 12, 2018, Luitpol Pharmaceuticals, Inc., submitted a 505(b)(2) New Drug Application (NDA 209379) for selenious acid injection as a source of selenium for parental nutrition when oral or enteral nutrition is not possible, insufficient or contraindicated. Selenious acid injection has been available for over 30 years as an unapproved marketed product. The application is relying on published literature for approval. The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the Pregnancy and Lactation subsections of labeling for formatting recommendations.

Selenious acid is a selenium compound and is used as a source of selenium. Selenious acid has the following characteristics:[1]

- Selenious acid injection provides 60 mcg of selenium[1]
- Primarily eliminated in the urine (b) (4)[1]
- (b) (4)
- Selenite is an inorganic form of selenium and the selenite anion is a selenium oxoanion[2]
- Absorption of selenite following oral administration is approximately 40-70%[2]
- Elimination is mainly through the urine[2]
- Absorbed selenium from inorganic sources, such as selenite and organic sources, including selenomethionine are both metabolized to hydrogen selenide, and are subsequently incorporated into essential selenoproteins[2]
- Molecular weight = 128.984 g/mol[2]

REVIEW

PREGNANCY

Selenium Deficiency and Pregnancy

Selenium is an essential trace element needed to prevent selenium deficiency. Selenious acid is the acid form of sodium selenite, a form of selenium. Selenium is found in a variety of foods and plants and is required for all ages in trace amounts; however, in large quantities, selenium can be toxic.[3] See Table 1 below for the recommended dietary allowances for selenium for pediatrics, adults, pregnancy and lactation.

[1] NDA 209379, proposed package insert for selenious acid, submitted , November 7, 2018.
[2] Selenious Acid. National Institutes of Health, U.S. National Library of Medicine, National Center for Biotechnology Information, Compound summary for CID 1091, https://pubchem.ncbi.nlm.nih.gov/compound/selenious_acid#section=Top, accessed 18 January 2019.
[3] Prabhu K and X Li, 2016, Selenium, American Society for Nutrition, Adv Nutr 7:415-7. doi:10.3945/an.115.010785

Table 1. Recommended Dietary Allowances (RDAs) for Selenium (corresponds to Table 1, National Institute of Health, Office of Dietary Supplements, Selenium Face Sheet for Health Professionals)[7]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	15 mcg*	15 mcg*		
7–12 months	20 mcg*	20 mcg*		
1–3 years	20 mcg	20 mcg		
4–8 years	30 mcg	30 mcg		
9–13 years	40 mcg	40 mcg		
14–18 years	55 mcg	55 mcg	60 mcg	70 mcg
19–50 years	55 mcg	55 mcg	60 mcg	70 mcg
51+ years	55 mcg	55 mcg		

*Adequate Intake (AI)

Selenium functions via proteins called selenoproteins, the most important selenoprotein being glutanthione peroxidase (GSH-Px) which is important for defending against oxidative stress. Selenium is also thought to have anti-inflammatory properties. Selenium deficiency has been reported in patients receiving parenteral nutrition which lacks selenium.[4] Selenium deficiency can exacerbate iodine deficiency, potentially increasing the risk of cretinism in infants. Symptoms of selenium deficiency include fatigue, muscle weakness, muscular pain and inflammation, hypothyroidism, Keshan disease[5], enlargement of the heart, cardiac arrhythmia, Kashin-Beck disease[6], joint pain, swollen joints, cretinism, mental retardation, growth retardation, hair and skin discoloration.[7]

According to published literature, selenium deficiency may cause complications in female reproduction and adverse pregnancy outcomes.[8] According to published literature, selenium concentrations decrease in pregnant women when compared to non-pregnant women.[9] In a case-control study including 14 pregnant women whose pregnancies were terminated as a result of neural tube defects (NTDs) diagnosed during the second trimester, Cengiz et al. (2004), concluded that there may be a positive correlation between low concentrations of selenium in pregnant woman and the occurrence of neural tube defects; however, the number of subjects in the study was very low and the authors state that the number of NTDs may be due to a combination of trace element deficiencies and not isolated to just one and could be due to overall poor nutrition.[10]

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[4] Jin J et al., 2017, Trace Elements in Parenteral Nutrition: Considerations for the Prescribing Clinician, Nutrients, 9 (440): 1-11.
[5] Keshan disease: congestive cardiomyopathy caused by dietary deficiency of selenium and the presence of a mutated strain of Coxsackievirus.
[6] Kashin-Beck disease: necrotizing osteochondropathy due to mineral trace deficiency (selenium and iodine)
[7] Selenium. National Institutes of Health, Office of Dietary Supplements, https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/, accessed 11 January 2019.
[8] Pieczynska J and H Grajeta, 2015, The role of selenium in human conception and pregnancy, Journal of Trace Elements in Medicine and Biology, 29:31-38.
[9] Wasowicz W et al., 1993, Plasma trace element(Se,Zn,Cu) concentration in maternal and umbilical cord blood in Poland, BiolTraceElemRes,38:205–15.
[10] Cengiz B et al., 2004, Serum zinc, selenium, copper and lead levels in women with second-trimester induced abortion resulting from neural tube defects, Biol Trace Elem Res, 97:225–35.

In addition, published literature has reported increases in pre-eclampsia, pre-term delivery, miscarriage, cholestasis, gestational diabetes and thyroid dysfunction with selenium deficiency in pregnancy.[11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] It should also be noted that exposure to tobacco and alcohol can also lead to decreases in selenium levels.[31,32,33,34] See Table 1 in Appendix A for selenium levels reported in publications with pregnancy-related complications.

[11] Ghaemi SZ et al., 2013, A prospective study of selenium concentration and risk of preeclampsia in pregnant Iranian women: a nested case–control study, Biol Trace Elem Res, 152:174–9.
[12] Rayman MP et al., 2003, Redman CWG. Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom. Am J Obstet Gynecol,189:1343–9.
[13] Gromadzinska J et al., 1998, Selenium levels, thiobarbituric acid-reactive substance concentrations and glutathione peroxidase activity in the blood of women with gestosis and imminent premature labour, Analyst, 123:35–40.
[14] Mahomed K, et al., 2000, Leukocyte selenium, zinc, and copper concentrations in preeclamptic and normotensive pregnant women, Biol Trace Elem Res, 75(1–3): 107–18.
[15] Bogden DJ et al., 2006, Low- normal serum selenium early in human pregnancy predicts lower birth weight, Nutr Res, 26:497–502.
[16] Barrington JW et al., 1996, Selenium deficiency and miscarriage: a possible link? Br J Obstet Gynaecol, 103:130–2.
[17] Al-Kunani AS et al., 2001, The selenium status of women with a history of recurrent miscarriage, Br J Obstet Gynaecol,108:1094–7.
[18] Kumar KSD et al., 2002, Role of red cell selenium in recurrent pregnancy loss, J Obstet Gynaecol, 22(2):181–3.
[19] Zachara BA et al., 2001, Blood selenium and glutathione peroxidases in miscarriage, Br J Obstet Gynaecol, 108:244–7.
[20] Reyes H et al., 2000, Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in nor-mal pregnancies and in healthy individuals in Chile, J Hepatol, 32:542–9.
[21] Kauppila A et al., 1987, Low serum selenium con- centration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy, BMJ, 294:150–2.
[22] Steinbrenner H et al, 2011, High selenium intake and increased diabetes risk: experimental evidence for interplay between selenium and carbohydrate metabolism, J Clin Biochem Nutr, 48(1):40–5.
[23] Tan M et al., 2001, Changes of serum selenium in pregnant women with gestational diabetes mellitus, Biol Trace Elem Res, 83:231–7.
[24] Al-Saleh E et al., Maternal–fetal status of copper, iron, molybdenum, selenium and zinc in insulin-dependent diabetic pregnancies, Arch Gynecol Obstet, 271:212–7.
[25] Escobar GM et al., 2004, Maternal thyroid hormones early in pregnancy and fetal brain development, Best Pract Res Clin Endocrinol Metab, 18(2):225–48.
[26] Klinger G et al., 1999, Parenteral selenium supplementation in extremely low birth weight infants: inadequate dosage but no correlation with hypothyroidism, J Perinatol, 19:568–72.
[27] Negro R et al., 2007, The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies, J Clin Endocrinol Metab, 92:1263–8.
[28] Abdulah R et al., 2013, Reduced serum selenium concentration in miscarriage incidence of Indonesian subjects, Biol Trace Elem Res, 154:1–6.
[29] Kosanovic M et al., 2002, Maternal and fetal cadmium and selenium status in normotensive and hypertensive pregnancy, Biol Trace Elem Res, 89:97–103.
[30] Mistry HD et al., 2008, Reduced selenium concentrations and glutathione peroxidase activity in preeclamptic pregnancies, Hypertension, 52:881–8.
[31] Mathews F et al., 2000, Nutrient intakes during pregnancy: the influence of smoking status and age, J Epidemiol Community Health, 54:17–23.
[32] Wisborg K et al., 1996, Smoking during pregnancy and preterm birth, Br J Obstet Gynaecol, 103:800–5.
[33] Kantola M et al., 2004, Selenium in pregnancy: is selenium an active defective ion against environ- mental chemical stress? Environ Res, 96:51–61.
[34] Halmesmäki E et al., 1986, Selenium in pregnancy: effect of maternal drinking, Obstet Gynecol, 68(5):602–5.

Nonclinical Experience

Animal reproduction studies have not been conducted with selenious acid injection.

Review of Pharmacovigilance Database

The applicant conducted a search of their pharmacovigilance database. The Luitpold pharmacovigilance database has reportable events that date back to 2006. The search revealed 11 total cases; however, none of the reports included pregnancy, drug exposure in utero, exposure during breastfeeding/lactation and male infertility.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature regarding selenium exposure during pregnancy. [27,35,36,37,38,39,40,41,42,43,44] These publications evaluated the safety and effectiveness of selenium supplementation in pregnant women. Selenium supplementation was given in these publications for a variety of reasons including to reduce pre-eclampsia risk in selenium-deficient pregnant women, to evaluate the effectiveness of selenium supplementation on insulin resistance during pregnancy, to evaluate the effectiveness of selenium supplementation on the improvement of reproductive outcomes, inflammation and oxidative stress in women with polycystic ovarian syndrome and as a supplement to reduce oxidative stress during pregnancy. In the majority of publications, there appears to be little or no difference between treatment and control groups. Only one publication, Sudfeld (2014)[40], reported a concern with selenium supplementation while breastfeeding; the authors noted that there was an increase in detectable HIV-1 RNA in the breastmilk of HIV infected mothers. Overall, the applicant concluded that selenium supplementation appears to be safe in healthy pregnant and lactating women.

[35] Rayman M et al., 2014, Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: a randomized, controlled pilot trial, British Journal of Nutrition, 112:99-111.
[36] Tara F et al., 2010, Selenium Supplementation and the Incidence of Preeclampsia in Pregnant Iranian Women: A Randomized, Double-blind, Placebo-controlled Pilot Trial, Taiwan J Obstet Gynecol, 49(2):181-187.
[37] Tara F et al., 2010, Prooxidant-antioxidant balance in pregnancy: a randomized double-blind placebo-controlled trial of selenium supplementation, 38:473-478.
[38] Mokhber et al. 2011, Effect of supplementation with selenium on postpartum depression: a randomized double-blind placebo-controlled trial, J Matern Fetal Neonatal Med, 24(1):104-8.
[39] Rayman MP et al., 2015, Selenium status in U.K. pregnant women and its relationship with hypertensive conditions of pregnancy, Br J Nutr, 113(2):249-58.
[40] Sudfeld CR et al., 2014, Effect of selenium supplementation on HIV-1 RNA detection in breast milk of Tanzanian women, Nutrition, 30(9):1081-4.
[41] Tara F et al., 2010, Selenium supplementation and premature (pre-labour) rupture of membranes: A randomized double-blind placebo-controlled trial, Journal of Obstetrics and Gynaecology, 30(1):30-34.
[42] Asemi Z et al., 2015, Effects of selenium supplementation on glucose homeostasis inflammation, and oxidative stress in gestational diabetes: Randomized, double-blind, placebo-controlled trial, Nutrition, 31(10):1235-1242.
[43] Mao J et al., 2016, Genetic polymorphisms that affect selenium status and response to selenium supplementation in United Kingdom pregnant women, Am J Clin Nutr, 103(1):100-6.
[44] Mao J et al., 2016, No effect of modest selenium supplementation on insulin resistance in UK pregnant women, as assessed by plasma adiponectin concentration, Br J Nutr, 115(1):32-8.

Table 2. Summary adverse events of selenium supplementation in pregnant and lactating women submitted by the applicant (corresponds with Table 8, page 71 of applicant's submission)

Pregnant women	
Asemi et al., 2015	"No side effects were reported after selenium administration in the study patients."
Mao et al., 2016	Not reported
Mao et al., 2016	Not reported
Mokhber et al., 2011	Not reported
Negro et al., 2007	None reported: "During the study period, no adverse effects due to excess Se intake were observed in the Se-treated group."
Rayman et al., 2014	2 adverse events were reported: one rash on the legs below the knees, deemed to be mild, and possibly related to the study treatment. Another had spontaneous torsion of her right ovary that required right oophorectomy, a rare complication of pregnancy, not connected with the study supplement.
Rayman et al., 2015	Not reported
Sudfeld et al., 2014	The effect of selenium supplementation on breast milk shedding of HIV-1 variedby receipt of HAART and parity. Detectable HIV-1 RNA in breast milk: 36.4% detectable HIV-1 RNA (37.8%) among women without HAART). In controls, 27.5% detectable HIV-1 RNA (27.5% among women without HAART).
Tara et al., 2010A	Supplementation with selenium was not associated with any reported major side effects
Tara et al., 2010B	Obstetrical outcomes for caesarean section rates and gestational age did not differ significantly between groups
Tara et al., 2010C	22 participants withdrew from selenium group (2 with intolerance to selenium, 1 with Metrorrhagia.); 19 withdrew from placebo group (2 with intolerance, 1 with spotting)

DPMH Review of Literature
DPMH conducted a search of published literature using PubMed and Embase regarding selenium exposure during pregnancy using the following search terms, "selenium and fetal malformations," "selenium and spontaneous abortion and miscarriage," "selenium embryo-fetotoxicity. No additional data were found.

According to Micromedex[45] selenium is safe to use during pregnancy.

Reviewer comment: The applicant's review of literature is adequate.

LACTATION
Nonclinical Experience
Animal reproduction studies have not been conducted with selenious acid injection.

Review of Pharmacovigilance Database
The applicant conducted a search of their pharmacovigilance database. The Luitpold pharmacovigilance database has reportable events that date back to 2006. No reports were found with regard to breastfeeding/lactation.

[45] Selenium. https://www.micromedexsolutions.com/micromedex2/librarian/CS/5362C6/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/E71B1E/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=selenium&UserSearchTerm=selenium&SearchFilter=filterNone&navitem=searchALL#, accessed 14 January 2019.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of literature and concluded that there are no adequate studies with regard to lactation.

DPMH's Review of Literature

DPMH conducted a search of *Medications in Mother's Milk*[46], the Drugs and Lactation Database (LactMed),[47] Micromedex, *Drugs in Pregnancy and Lactation* by Briggs and Freeman, and of the published literature in PubMed and Embase using the search terms "selenious acid injection" and the following terms, "lactation," or "breast-feeding." There is no available information in LactMed.

Several published studies have determined that selenium is naturally present in human milk. Dorea (2002),[48] provided a review article of selenium nutrition during breast-feeding which includes environmental and maternal selenium supplemental concentrations in breastmilk. Tables 2, 3 and 4 in Appendix A contains a summary of each of the published studies reviewed by the author showing selenium concentrations collected. Amounts of selenium in breastmilk appear to differ depending on the type of selenium supplementation used [e.g., organic versus inorganic (selenite, selenite seen in maternal supplements) versus dietary (naturally occurring in foods)]. According to Dorea (2002), selenium appears in breastmilk as a component of seleno-proteins and selenoamino-acids in milk proteins and are well tolerated by breastfed infants; however, organic selenium supplementation was not detected in breastmilk.

Li et al. (2016),[49] examined the breastmilk of mineral and trace element concentrations of *Mam*-Mayan Guatemalan women at 3 stages of lactation [transitional milk 5-17 days post-partem (n=56), early milk 18-46 days post-partum (n=75) and established milk 4-6 months postpartum (n=103)]. The study compared the mineral and trace element concentrations and their percent of estimated intake divided by Adequate Intake (AI) across all three stages of lactation. The study was conducted from June 2012 to January 2013 in eight rural *Mam*-Mayan communities of Guatemala. Breastmilk was collected in the morning via manual expression by a trained midwife. Selenium ranged from 48% to 60% of the AI but did not differ by stage of lactation or by gender.

According to breastfeeding expert, Thomas Hale PhD, in *Medications and Mothers' Milk*,[46] selenium dietary supplement is needed for antioxidant enzymes and has an RDA of 70 µg/day for breastfeeding women. There is no information on relative infant dose or effects of selenium on the breastfed infant.

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[46] Hale, Thomas (2017). Medications and Mother's Milk. Amarillo, Texas. Springer Publishing Company LLC.

[47] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[48] Dorea J, 2002, Selenium and breast-milk review article, British Journal of Nutrition, 88:443-461.

[49] Li C et al., 2016, Minerals and Trace Elements in Human Breast Milk Are associated with Guatemalan Infant Anthropometric Outcomes within the First 6 Months, J Nutr, 146:2067-74.

According to Micromedex,[45] selenium is "safe to consume during lactation."

Reviewer comment: The applicant's submission did not include published literature with regard to selenious acid injection and breastmilk. DPMH conducted a review of published literature and notes that according to published literature, selenium is present in human breastmilk in various amounts depending on the type of supplementation.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal reproduction studies have not been conducted with selenious acid injection.

Review of Pharmacovigilance Database

The applicant conducted a search of their pharmacovigilance database. The Luitpold pharmacovigilance database has reportable events that date back to 2006. No reports were found with regard to females and males of reproductive potential.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature, and no data were submitted with regard to selenious acid injection and females and males of reproductive potential.

DPMH's Review of Literature

DPMH conducted a review of published literature using Embase and PubMed for selenious acid injection and effects in females and males of reproductive potential, and no data were found. However, according to published literature a selenium deficiency may cause effects on fertility as discussed earlier in the review.

Reviewer comment: The applicant's review is sufficient.

DISCUSSION AND CONCLUSIONS

Pregnancy

Selenium is an essential trace element needed to prevent selenium deficiency. Although animal reproduction studies have not been conducted with selenious acid injection, the product has been used in humans for decades. According to published literature, there have been reported increases in pre-eclampsia, pre-term delivery, miscarriage, cholestasis, gestational diabetes and thyroid dysfunction with selenium deficiency in pregnancy. According to the National Institutes of Health, the recommended daily allowance of selenium is 60 mcg (see Table 1 above).[7] In addition, Micromedex notes that selenium is safe to administer during pregnancy in trace amounts. Selenious acid injection is primarily used as a source of selenium in parenteral nutrition and is not expected to be harmful during pregnancy as there are no reports of adverse pregnancy outcomes due to selenious acid supplementation in parenteral nutrition in pregnant women.

Lactation
Selenium is an essential trace element that present in breastmilk in various amounts based on selenium dietary and supplementation intake. There is no information on the effects of selenium on the breastfed infant; however, according to Micromedex, selenium is safe to use during breastfeeding.

Females and Males of Reproductive Potential
There are no data on the effects of selenium on fertility; however, as discussed in the review a deficiency in selenium may cause effects on fertility.

LABELING RECOMMENDATIONS
DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Administration of the approved recommended dose of Selenious Acid Injection in parenteral nutrition is not expected to cause major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with Selenious Acid Injection.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary
Selenium is present in human milk. Administration of the approved recommended dose of Selenious Acid Injection in parenteral nutrition is not expected to cause harm to a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Selenious Acid Injection and any potential adverse effects on the breastfed infant from Selenious Acid Injection or from the underlying maternal condition.

Appendix A.

Table 1. Publications from published literature reporting selenium levels and pregnancy-related complications (adapted frrom Table 3 found on page 6 of Pieczynska J and H Grajeta 2015)

Publication	Selenium assessment technique	Country	Case subjects	Selenium concentration (µgSe/L)	Non-case subjects	Selenium concentration (µgSe/L)
Abdulah (2013)[28]	Serum (fluorimetry)	Indonesia	Spontaneous miscarriage	66.71 (n = 25)[a]	Normal pregnancies	76.36(n = 46)
Barrington (1996)[16]	Serum (AAS)[b]	South Wales	Spontaneous miscarriage	54.48 (n = 40)	Normal pregnancies	65.29(n = 40)
Kumar (2002)[18]	Red cells(fluorimetry)	India	Non-pregnant women with recurrent miscarriage	119.55 (n = 20)	Healthy non-pregnant women	150.55 (n=20)
Kosanovic (2002)[29]	Whole blood (AAS)	Yugoslavia	Hypertensive pregnant women	54.65 (n = 23)	Normotensive pregnant women	57.5 (n-37)
Al-Saleh (2005)[24]	Whole blood (AAS)	Kuwait	Diabetic pregnant women	85.65 (n = 14)	Healthy pregnant women	102.65 (n=17)
Reyes (2000)[20]	Plasma (AAS)	Chile	Intrahepatic cholestasis pregnant women	78.43 (n = 21)	Healthy pregnant women	92.22 (n=98)
Kauppila (1987)[21]	Serum (AAS)	Finland	Intrahepatic cholestasis pregnant women	27.65 (n=12)	Healthy pregnant women	41.65 (n=12)
Ghaemi (2013)[11]	Plasma (GFAAS)	Iran	Pregnant women with pre-clampsia	71.22 (n = 38)	Healthy pregnant women	80.27 (n=38)
Rayman (2003)[12]	Toenail (INAA) (mg/kg)	United Kingdom	Pregnant women with pre-clampsia	0.56 (n = 53)	Healthy pregnant women	0.62 (n=53)
Mistry (2008)[30]	Serum (AAS)	United Kingdom	Pregnant women with pre-clampsia	39.7 (n = 25)	Healthy pregnant women	58.4 (n=25)
Negro (2007)[27]	Whole blood (AAS)	Italy	Euthyroid pregnant women	75.7 (n = 74)	Healthy pregnant women	76.8 (n=81)

a Mean (number of samples).

b AAS, atomic absorption spectrometry; GFAAS, graphite furnace atomic absorption spectrometry; INAA, instrumental neutron activation analysis.

Table 2. Summary of studies reporting mean selenium concentrations (μg/l or μg/kg) and glutathione peroxidase (GPX) activity in breast milk. (corresponds to Table 1, page 444, Dorea 2002)[48]

Reference	Country	Se concentration	GPX activity (units)	Stage of lactation	Observations
Al-Awadi & Srikumar (2001)	Kuwait	20·0	182·0	0–6 m	Kuwaiti
		18·0	130·0	0–6 m	Non-Kuwaiti
		16·0	126·0	6–12 m	Kuwaiti
		16·0	115·0	6–12 m	Non-Kuwaiti
		15·0	128·0	12–18 m	Kuwaiti
		14·0	104·0	12–18 m	Non-Kuwaiti
Debski *et al.* (1987)	USA	15·1	36·0	NG	
Debski *et al.* (1989)	USA	22·2	40·1	4–6 m	Vegetarian
		16·8	27·5	4–6 m	Non-vegetarian
Dodge *et al.* (1998)	China	22·6	70·0	Early	Xichang
		6·3	40·0	Late	Xichang
		26·0	78·0	Early	Beijing
		15·8	68·0	Late	Beijing
		83·0	69·0	Early	Enshi
		94·8	61·0	Late	Enshi
Dodge *et al.* (1999)	New Zealand	12·9	34·0	1–90 d	Supplemented
		9·4	39·0	1–90 d	Non-supplemented
Ellis *et al.* (1990)	USA	32·4	29·7	3 d	Term
		26·0	36·8	7 d	Term
		23·7	39·2	21 d	Term
		21·3	35·4	42 d	Term
		31·6	39·7	3 d	Preterm
		26·8	28·8	7 d	Preterm
		25·3	30·1	21 d	Preterm
		22·9	33·2	42 d	Preterm
		32·4	28·2	3 d	Very preterm
		26·0	28·2	7 d	Very preterm
		24·5	22·9	21 d	Very preterm
		25·3	29·5	42 d	Very preterm
Funk *et al.* (1990)	Gambia	21·0	51·0	Early	Dry season
		19·4	40·8	Late	Dry season
Hojo (1986)	Japan	34·2	66·0	4 d	
		24·0	46·0	7–8 d	
		22·5	38·8	36–86 d	
Hojo (1987)	Japan	22·5	38·8	1–3 months	
L'Abbe & Friel (2000)	Canada	NG	73·0	1–12 weeks	Term
		NG	85·8	1–12 weeks	Preterm
Mannan & Picciano (1987)	USA	15·6	68·1	4–16 weeks	Fore-milk
		18·1	90·4	4–16 weeks	Hind-milk
Milner *et al.* (1987)	USA	14·4	136·0	1–12 months	

Moore *et al.* (2000)	China	7·4	54·0	1 d	Control
		8·7	80·0	1 week	Control
		9·3	88·0	2 weeks	Control
		11·7	91·0	3 weeks	Control
		8·4	82·0	4 weeks	Control
		6·3	19·0	12 weeks	Control
		16·7	70·0	1 d	100 mg selenomethionine/d
		17·9	90·0	1 week	100 mg selenomethionine/d
		19·8	88·0	2 weeks	100 mg selenomethionine/d
		16·9	90·0	3 weeks	100 mg selenomethionine/d
		16·2	83·0	4 weeks	100 mg selenomethionine/d
		9·9	45·0	12 weeks	100 mg selenomethionine/d
Trafikowska *et al.* (1996)	Poland	9·2	82·7	1 month	
		15·9	80·7	1 month	200 mg yeast Se/d
		15·0	92·7	2 months	200 mg yeast Se/d
		14·4	74·9	3 months	200 mg yeast Se/d
Trafikowska *et al.* (1998)	Poland	8·9	80·0	0 months	Control
		8·9	75·0	0 months	Yeast Se
		8·9	70·0	0 months	Selenite
		8·9	71·0	1 month	Control
		16·0	72·0	1 month	Yeast Se
		12·9	90·0	1 month	Selenite
		9·0	72·0	2 months	Control
		14·5	80·0	2 months	Yeast Se
		13·0	145·0	2 months	Selenite
		6·0	80·0	3 months	Control
		13·0	70·0	3 months	Yeast Se
		14·0	150·0	3 months	Selenite
Williams (1983)	New Zealand	7·6	31·0	29–33 d	

NG, not given; m, months.

Table 3. Summary of studies comparing mean selenium concentrations (µg/l or µg/kg) in fore-and hind-milk (corresponds to Table 2, page 445, Dorea 2002)[48]

Reference	Country	Fore-milk	Hind-milk	Stage of lactation	Observations
Bratter *et al.* (1991*b*)	Germany	NG	NG	NG	16 % increase in hind-milk
Cumming *et al.* (1983)	Australia	11·8	–	8–23 weeks	Users and non-users of oral contraceptives, fore-milk
Cumming *et al.* (1992*b*)	Australia	–	12·0	6–12 weeks	Boys
		–	12·5	6–12 weeks	Girls
Cumming *et al.* (1992*a*)	Australia	10·8	13·9	6–12 weeks	
Dorner *et al.* (1990)	Germany	31·0	–	2 weeks	
		24·3	–	5 weeks	
		21·3	–	8 weeks	
		18·7	–	12 weeks	
		17·6	–	16 weeks	
Mandic *et al.* (1995)	Croatia	11·3	10·4	1 week – 60 d	Smokers
		11·5	10·2	1 week – 60 d	Two deliveries
		–	11·9	1 week – 60 d	Two deliveries
Mannan & Picciano (1987)	USA	15·6	18·1	4–16 weeks	
Smith *et al.* (1982)	USA	15·7	16·3	2 weeks	
		14·4	15·2	1 month	
		14·1	15·9	2 months	
		13·9	16·4	3 months	
Walivaara *et al.* (1986)	Sweden	14·3	14·2	NG	

NG, not given.

Table 4. Summary of studies that measured selenium concentrations in breastmilk and maternal plasma or serum (corresponds to Table 3, page 446-447, Dorea 2002)[48]

		Mean Se concentration (mg/l)				
Reference	Country	Plasma or serum	Milk	Stage of lactation	Observations
Al–Awadi & Srikumar (2001)	South Arabia	126·0	20·0	0–6 months	Kuwaiti
		87·0	18·0	6–12 months	Kuwaiti
		79·0	16·0	12–18 months	Kuwaiti
		87·0	16·0	0–6 months	Non-Kuwaiti
		79·0	15·0	6–12 months	Non-Kuwaiti
		63·0	14·0	12–18 months	Non-Kuwaiti
Alegria *et al.* (1998)	Spain	74·7	9·6	NG	Whole blood
Arnaud *et al.* (1993*b*)	Niger	62·0	20·0	5 d	Serum
		89·0	15·0	90 d	Serum
		88·0	12·0	180 d	Serum
Arnaud *et al.* (1993*a*)	Niger	62·41	18·9	Colostrum	Serum
		60·83	19·8	Colostrum	Serum

		90·85	15·0	3 months	Serum
		90·85	14·2	3 months	Serum
		89·27	11·9	6 months	Serum
		90·0	13·4	6 months	Serum
Bratter *et al.* (1997)	Venezuela	229·0	42·9	20–24 d	Yaracuy, serum
		327·0	56·6	20–24 d	Portugueza 1 region
		621·0	112·2	20–24 d	Portugueza 1 region
Cumming *et al.* (1992*b*)	Australia	81·0	11·9	6–12 weeks	Serum
Cumming *et al.* (1983)	Australia	77·4	11·8	8–23 weeks	Plasma
Dodge *et al.* (1998)	China	15·8	6·3		Plasma, Xichang
		86·8	15·8		Plasma, rural Beijing
		552·7	94·8		Plasma, Enshi
Grandjean *et al.* (1995)	Faroe Islands	NG	19·1	NG, transitional milk	
Higashi *et al.* (1983)	Japan	148·0	17·0	3 months	Serum
Hojo (1987)	Japan	153·3	4·2	1–3 months	
Kantola *et al.* (1997)	Finland	11·8	22·1	Colostrum	Serum
	Estonia	63·0	13·1	Colostrum	Serum, Rakvere
	Estonia	48·2	11·2	Colostrum	Serum, Tallin
	Russia	88·3	21·9	Colostrum	Serum
Kumpulainen *et al.* (1985)	Finland	55·0	11·0	5–6 d	Unsupplemented
		84·0	10·4	4 months	Unsupplemented
		54·0	11·6	5–6 d	Selenite supplemented
		105·0	11·0	4 months	Selenite supplemented
		56·0	11·6	5–6 d	Yeast Se supplemented
		142·0	13·4	5–6 d	Yeast Se supplemented
Levander *et al.* (1987)	USA	136·0	20·0	1 month	Plasma
		137·0	15·0	3 months	Plasma
		138·0	15·0	6 months	Plasma
Mannan & Picciano (1987)	USA	97·0	16·8	4–16 weeks	
Micetic-Turk *et al.* (2000)	Slovenia	62·0	29·0	2–3 d	Serum
Michalke & Schramel (1998)	Austria	70·0	15·8	NG	
Moore *et al.* (2000)	China	35·0	7·4	1 d	Control
		–	8·7	1 week	Control
		48·0	9·3	2 weeks	Control
		–	11·7	3 weeks	Control
		50·0	8·4	4 weeks	Control
		30·0	6·3	12 weeks	Control
		100·0	16·7	1 d	100 mg selenomethionine/d
		–	17·9	1 week	100 mg selenomethionine/d
		88·0	19·8	2 weeks	100 mg selenomethionine/d
		89·0	16·9	3 weeks	100 mg selenomethionine/d
		80·0	16·2	4 weeks	100 mg selenomethionine/d
		–	9·9	12 weeks	100 mg selenomethionine/d
Moser *et al.* (1988)	Nepal	8·2*	10·0	2–6 months	
	USA	17·4*	15·0	NG	
Rossipal *et al.* (2000)	Austria	69·5	32·7	1 d	Serum
Schramel *et al.* (1988*a*)	Germany	80·0	43·0	1 d	Whole blood
		–	21·0	Mature milk	
Trafikowska *et al.* (1996)	Poland	54·0	9·2	1 d	Baseline, plasma
		101·0	15·9	1 month	200 mg Se/d, plasma
		127·0	15·0	2 months	200 mg Se/d, plasma
		116·0	14·4	3 months	200 mg Se/d, plasma

Trafikowska *et al.* (1998)	Poland	50·0	8·9	0 months	Control
		50·0	8·9	0 months	Yeast Se
		50·0	8·9	0 months	Selenite
Wasowicz *et al.* (2001)	Poland	50·0	8·9	1 month	Control
		105·0	16·0	1 month	Yeast Se
		90·0	12·9	1 month	Selenite
Williams (1983)	New Zealand	50·0	9·0	2 months	Control
		130·0	14·5	2 months	Yeast Se
		100·0	13·0	2 months	Selenite
		49·0	6·0	3 months	Control
		115·0	13·0	3 months	Yeast Se
		100·0	14·0	3 months	Selenite
		34·9	22·8	0–4 d	Plasma
		44·6	11·3	5–9 d	Plasma
		54·3	9·2	10–30 d	Whole blood
		46·0	7·6	29–35 d	

NG, not given.

* nmol/l.

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