CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022485Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22485/000	**Sponsor:**	SANDOZ
Org. Code:	161		2555 WEST MIDWAY BLVD
Priority:	5		BROOMFIELD, CO 80038
Stamp Date:	17-MAR-2010	**Brand Name:**	ARGATROBAN INJECTION 1 MG/ML
PDUFA Date:	17-JAN-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:		**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION, INJECTION; ARGATROBAN; 1MG/125ML

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	R. KASLIWAL	Review Chemist	301-796-1386
	J. BROWN	Team Leader	301-796-1652

Overall Recommendation:	ACCEPTABLE	on 09-SEP-2010	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 09-JUN-2010	by M. STOCK	(HFD-320)	301-796-4753

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

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Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JUN-2010

Deci ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9615155 **FEI:** 3000280957

SANDOZ CANADA INC
145 JULES-LEGER STREET

BOUCHERVILLE, QC, CANADA

DMF No:

AADA: N 020883

I 101957

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: (b) (4)

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAY-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUL-2010

Decision: ACCEPTABLE

Reason: BASED ON FILE REVIEW

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/s/

NIKOO N MANOCHEHRI-KALANTARI
05/18/2011

NDA 22-485

Argatroban Injection
In 0.9% Sodium Chloride
1 mg/mL

Sandoz Canada Inc.,
Alison Sherwood, c/o Sandoz Inc.,
2555 W. Midway Blvd.,
P.O. Box 446,
Broomfield, CO 80038

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment –III
Division of Hematology Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 22-485**

2. REVIEW #: 1

3. REVIEW DATE: 21-Dec-2010

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Mar-2010
Amendment (QR)	30-Apr-2010
Amendment (QR)	12-Jul-2010
Amendment (QR)	29-Jul-2010
Amendment (QR)	19-Nov-2010
Amendments (QR & BL)	17-Dec-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Canada Inc.
Address:	2555 W. Midway Blvd., P.O. Box 446 Broomfield, CO 80038
Representative:	Alison Sherwood, c/o Sandoz Inc.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Argatroban Injection
c) Code Name/# (ONDC only): +AGT [redacted] (b) (4); 1006435 (Sandoz)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Anticoagulant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1 mg/mL

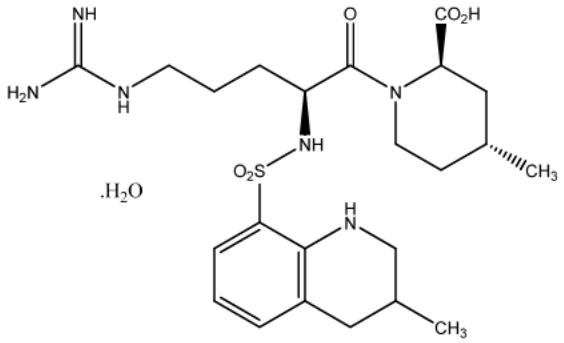
13. ROUTE OF ADMINISTRATION:

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(1) 2-Piperidinecarboxylic acid, 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-, monohydrate; **(2)** (2*R*,4*R*)-4-Methyl-1-[N^2-[(1,2,3,4-tetrahydro-3-methyl-8-quinolyl)sulfonyl]-L-arginyl] pipecolic acid, monohydrate.



Chemical Formula: $C_{23}H_{36}N_6O_5S$
Molecular Weight: 508.63
Elemental Analysis: C, 54.31; H, 7.13; N, 16.52; O, 15.73; S, 6.30

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Argatroban	3	Adequate	19-Nov-2008	DMF was reviewed by Dr. Mark Sassaman and was found to be adequate.
	III		(b) (4)	4	NA	NA	NA
	III			7, 3	See Micro	See Micro	The DMF describes (b) (4)

		(b) (4)		Review	Review	(b) (4). See micro Review for validation assessment.
(b) (4)	III		3	Adequate	19-May-2004	DMF was reviewed by Dr. Rapti Madhurawe for injectable solution and was found to be adequate.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		Injectable product.
EES	Acceptable	09-Sep-2010	M. Stock, Office of Compliance.
Pharm/Tox	Approval	20-Dec-2010	Shwu Luan Lee, Ph.D.
Biopharm	Not Applicable		
LNC	Not applicable		Argatroban is an established name not an NME.
Methods Validation	Not Applicable		The analytical methods used are well established methods and a methods validation by FDA labs was not requested.
ODS / DMEPA	There is no trademark proposed. DEMEPA labeling comments were sent to the applicant.	See DMEPA review 13-Dec-2010	Yelena L Maslov
EA	Categorical claim for exemption is justified under 21CFR25.31 (a).	21-Dec-2010	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	21-Dec-2010	Stephen E. Langille, Ph.D.

The Chemistry Review for NDA 22-485

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, pending receipt of final and acceptable PI and container/carton labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The formulation of Argatroban Injection in Sodium Chloride 1 mg/mL is based on the information obtained from the outer label and package insert of the Reference Listed Drug (RLD), Argatroban Injection, manufactured by GlaxoSmithKline for Encysive Pharmaceuticals Inc. The qualitative difference between the two formulations is that Dehydrated Alcohol was removed from the Sandoz product to create a ready to use formulation. In the RLD, alcohol was needed to dissolve Argatroban, as the supplied solution contained 100 mg/ml of Argatroban in the supplied solution which was diluted to a 1 mg/ml solution at the site of use. The proposed formulation contains 1 mg/ml of Argatroban and does not need any further dilution.

(b) (4)

The finished Argatroban Injection is a sterile, non-pyrogenic, clear, and colorless to pale yellow isotonic solution. It is supplied in a single-use clear glass vial containing 125 mg of argatroban in 125 mL sodium chloride solution. Each mL contains 1 mg argatroban, 9 mg sodium chloride, USP, 3 mg sorbitol, NF in water for injection, USP. The pH of the solution is between 3.2 – 7.5

Based on submitted data, an **expiration dating period of 24-months** is may be approved, when the product is stored between 20ºC and 25ºC (See USP Controlled Room Temperature) in original container. The solution needs to be protected from light during storage and should not be kept in refrigerator of freezer, as at lower temperature argatroban may precipitate from solution. Due to this, I recommend that "Do not freeze" be prominently placed on the container / carton labels.

(b) (4)

Argatroban has 4 asymmetric carbons. One of the asymmetric

carbons has an *R* configuration (steroisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers in a ratio of approximately 65:35.
The solubility of the API is an important in the manufacturing process as the finished dosage form is a true solution. Argatroban is very slightly soluble in water. Studies performed at Sandoz Canada Inc. (b) (4)

A retest period of (b) (4) months was established by the drug substance manufacturer (b) (4). The Argatroban drug substance is re-tested by Sandoz Canada Inc. at (b) (4) months in line with the manufacturers until the expiration date of the drug substance.

B. Description of How the Drug Product is Intended to be Used

Argatroban Injection has been indicated to be used under two situations. One, it is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). Second, it is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

Argatroban is supplied as a ready to use solution for intravenous administration and no further dilutions are required or recommended. For HIT, a maximum of 3 doses are recommend during the procedure (75 mg within one surgery / day of 10 hours). For PCI use, a maximum of 3 doses are recommended during the procedure (560 mg within one surgery / day of 3hours).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an approval action (provided microbiology finds the product / process to be acceptable for sterilization and endotoxin controls) for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the Argatroban drug substance. Further the drug Master File (DMF) (b) (4), referencing the drug substance manufacturing and controls, has been assessed to be adequate.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are adequate to support the product application.
- The Office of Compliance has recommended that the drug substance and drug product manufacturing facilities are acceptable as of 09-Sep-2009 (see appendix 1).
- There are no outstanding issues with impurities.
- The microbiology reviewer has recommended approval (21-Dec-2010).

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist Name / Date: Ravindra K. Kasliwal, Ph.D.
Chemistry Team Leader Name / Date: Sarah Pope-Miksinski, Ph.D.
Project Manager Name / Date: Tu-Van Lee Lambert

C. CC Block: See DARRTS

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/s/

RAVINDRA K KASLIWAL
12/21/2010

SARAH P MIKSINSKI
12/21/2010

CMC DEFICIENCIES

1. Provide amended vial label that incorporates the following:

- Place the statement "For intravenous infusion only" below the statement "(1mg/mL) and delete the statement "FOR INTRAVENOUS USE" from the upper right corner.
- Place the statement "Single Use Vial" in the upper right corner opposite to the NDC number and delete the statement [redacted] (b) (4)
- Increase the prominence of the "Rx only" statement and move it below the strength statement.
- Chang the word "STERILE" to lower case to read "Sterile".
- Revise the content statement to: "Each milliliter contains: 1 mg argatroban, 9 mg sodium chloride, 3 mg sorbitol in water for injection, USP".
- Add "Protect from light" to the storage statement.

2. Provide amended carton labeling that incorporates the following:

- Place the statement "For intravenous infusion only" below the statement "(1mg/mL) and delete the statement "FOR INTRAVENOUS USE".
- Revise the content statement to: "Each milliliter contains: 1 mg argatroban, 9 mg sodium chloride, 3 mg sorbitol in water for injection, USP".
- Change and increase the prominence of the storage statement to "protect from light and store in original carton".
- Add "(See USP Controlled Room Temperature)" to the existing storage statement "Store at 20° – 25°C (68° – 77°F)".
- Delete the statement [redacted] (b) (4) from the front and back panels, and in its place add the statement "Package contains 2 single use vials".
- Increase the prominence of the "Rx only" statement and move it below the strength statement.

3. Provide amended drug product specifications that address the following:

- Change impurity [redacted] (b) (4)
- Report all impurities above 0.1%. Amend the specification to reflect this.
- It does not appear your method can sufficiently resolve impurities [redacted] (b) (4)

DMEPA DEFICIENCIES

A. Container Label and Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Place the name of diluents, Sodium Chloride or Dextrose, and their percent amounts on the principle display panel also immediately under the product's name to clearly differentiate the two Argatroban Products such as follows:

   Argatroban Injection
   in 0.9% Sodium Chloride
   125 mg/125 mL
   (1 mg/mL)

   Or

   Argatroban Injection
   in 5% Dextrose
   125 mg/125 mL
   (1 mg/mL)

   Additionally, to sufficiently distinguish between Argatroban in Sodium Chloride and Argatroban in Dextrose, print the name of the diluents and their percent amounts using contrasting colors and in the same font as the product's established name. As currently presented, the diluents blend with the other inactive ingredients on the side panel may be easily overlooked; thus, increasing the potential for selection error.

2. Place the statement "Do not dilute prior to administration" on the principle display panel to differentiate the dilution requirements from the reference listed drug, Argatroban Injection 250 mg/2.5 mL (100 mg/mL). The reference-listed drug (RLD), Argatroban Injection 250 mg/2.5 mL, is a concentrated solution that required dilution prior to administration. As a result, it is important to differentiate between the RLD and the new Argatroban Injection product, which does not require dilution prior to administration, to minimize medication errors associated with product's preparation for administration.

3. Add Bar Coding to the labeling per 21 CFR 201.25

4. Remove of the word "Sterile" from the principle display panel. This word is not important and clusters and labels and labeling.

5. Decrease the prominence of the "Rx Only" statement. As currently presented, it is as prominent as concentration statement and other pertinent information. Additionally, relocate the "Rx Only" statement to a less prominent location on the principle display panel such as upper right corner.

6. Delete the statement "Do not Freeze" because this statement is unnecessary and occupies space.

B. Container Labels for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Allocate the space on the vial label (e.g., the bottom of the principle display panel or the side panel) to place the product's name, diluent, strength, and concentration in the inverted manner to increase the readability of the label when the product is hung upside down.

2. Increase the prominence of the statement "For Intravenous Use" by relocating it from the side panel to the principle display panel under the product's concentration and increasing the font size.

3. Delete the phrase (b) (4) located immediately next to the statement "Single Use Vial" from the principle display panel because it is duplicative and clusters other important information.

4. Add the statement "Single Use Vial, Discard Unused Portion" to the principle display panel.

5. Revise the statements on the side panel regarding the ingredients contained in each milliliter of Argatroban Injection to improve clarity. As the statements currently presented, it is unclear whether each mL contains the particular amount of active and inactive ingredients or entire vial; thus, creating confusion that may lead to errors.

    a. Argatroban Injection in Sodium Chloride should be revised to state, "Each mL contains 1 mg argatroban, 9 mg sodium chloride, and 3 mg D-sorbitol".

    b. Argatroban Injection in Dextrose should be revised to state, "Each mL contains 1 mg argatroban, 50 mg dextrose, and 3 mg D-sorbitol".

C. Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection

125 mg/125 mL in Dextrose

1. Delete the phrase (b) (4) located under the statement "For Intravenous Use" from the principle display panels, because it is duplicative and distracts from the concentration.

2. Place the statement "Each Carton Contains 2 Single Use Vials" on the bottom of the principle display panels as well as upper and lower panels.

3. Increase the prominence of the statement “Protect from light and store in carton” in increasing the font size.

4. See comments in Sections B.4, which also apply to this Section.

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/s/

EBLA ALI IBRAHIM
12/21/2010

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- Increase the prominence of the "Rx only" statement and move it below the strength statement.
- Chang the word "STERILE" to lower case to read "Sterile".
- Revise the content statement to: "Each milliliter contains: 1 mg argatroban, 9 mg sodium chloride, 3 mg sorbitol in water for injection, USP".
- Add "Protect from light" to the storage statement.

2. Provide amended carton labeling that incorporates the following:

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- Revise the content statement to: "Each milliliter contains: 1 mg argatroban, 9 mg sodium chloride, 3 mg sorbitol in water for injection, USP".
- Change and increase the prominence of the storage statement to "protect from light and store in original carton".
- Add "(See USP Controlled Room Temperature)" to the existing storage statement "Store at 20° – 25°C (68° – 77°F)".
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3. Provide amended drug product specifications that address the following:

- Change impurity [redacted] (b) (4)
- Report all impurities above 0.1%. Amend the specification to reflect this.
- It does not appear your method can sufficiently resolve impurities [redacted] (b) (4) (RRT 1.45, RRT 1.46 and RRT 1.47) will be NMT 0.2% rather than for each one.

DMEPA DEFICIENCIES

A. Container Label and Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection 125 mg/125 mL in Dextrose

1. Place the name of diluents, Sodium Chloride or Dextrose, and their percent amounts on the principle display panel also immediately under the product's name to clearly differentiate the two Argatroban Products such as follows:

   Argatroban Injection
   in 0.9% Sodium Chloride
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   (1 mg/mL)

   Or

   Argatroban Injection
   in 5% Dextrose
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   (1 mg/mL)

   Additionally, to sufficiently distinguish between Argatroban in Sodium Chloride and Argatroban in Dextrose, print the name of the diluents and their percent amounts using contrasting colors and in the same font as the product's established name. As currently presented, the diluents blend with the other inactive ingredients on the side panel may be easily overlooked; thus, increasing the potential for selection error.

2. Place the statement "Do not dilute prior to administration" on the principle display panel to differentiate the dilution requirements from the reference listed drug, Argatroban Injection 250 mg/2.5 mL (100 mg/mL). The reference-listed drug (RLD), Argatroban Injection 250 mg/2.5 mL, is a concentrated solution that required dilution prior to administration. As a result, it is important to differentiate between the RLD and the new Argatroban Injection product, which does not require dilution prior to administration, to minimize medication errors associated with product's preparation for administration.

3. Add Bar Coding to the labeling per 21 CFR 201.25

4. Remove of the word "Sterile" from the principle display panel. This word is not important and clusters and labels and labeling.

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3. Delete the phrase (b) (4) located immediately next to the statement "Single Use Vial" from the principle display panel because it is duplicative and clusters other important information.

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    a. Argatroban Injection in Sodium Chloride should be revised to state, "Each mL contains 1 mg argatroban, 9 mg sodium chloride, and 3 mg D-sorbitol".

    b. Argatroban Injection in Dextrose should be revised to state, "Each mL contains 1 mg argatroban, 50 mg dextrose, and 3 mg D-sorbitol".

C. Carton Labeling for Argatroban Injection 125 mg/125 mL in Sodium Chloride and Argatroban Injection

125 mg/125 mL in Dextrose

1. Delete the phrase (b) (4) located under the statement "For Intravenous Use" from the principle display panels, because it is duplicative and distracts from the concentration.

2. Place the statement "Each Carton Contains 2 Single Use Vials" on the bottom of the principle display panels as well as upper and lower panels.

3. Increase the prominence of the statement “Protect from light and store in carton” in increasing the font size.

4. See comments in Sections B.4, which also apply to this Section.

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/s/

EBLA ALI IBRAHIM
12/10/2010