CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER REVIEW(S)

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Division of Pediatric and Maternal Health Review

Date: August 29, 2019 **Date consulted:** October 15, 2018
June 10, 2019

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Division of Dermatology and Dental Products (DDDP)

Drug: Absorica, Absorica LD (isotretinoin) capsules

NDA: 21951 S-13, 211913

Applicant: Sun Pharmaceutical Industries, Inc. (Sun)

Subject: Pregnancy and Lactation Labeling [NDA 21951: Prior Approval Supplement (PAS) for Pregnancy and Lactation Labeling Rule (PLLR) conversion, NDA 211913: Original 505(b)(2) NDA (new formulation-lower dosed product)]

Indication: Treatment of severe recalcitrant nodular acne in patients 12 years of age and older

Materials Reviewed:

- Applicant's background package for NDA 21951 S-13 submitted on September 7, 2018.
- Applicant's background package for NDA 211913 submitted on July 18, 2018.
- DPMH Review of iPledge Risk Evaluation and Mitigation Strategy (REMS) Pregnancy Testing and contraception requirements for Absorica. NDA 21951. Leyla Sahin, MD. May 3, 2017. DARRTS Reference ID 4092695.

Consult Question: The Division requests assistance with the review of the PLLR labeling.

INTRODUCTION AND BACKGROUND

- On July 18, 2018, the applicant (Sun) submitted a PAS (S-013) for Absorica (isotretinoin), NDA 21951 to comply with PLLR. DDDP consulted DPMH on October 15, 2018, to assist with the Pregnancy and Lactation subsections of labeling. This submission included a literature search and pharmacovigilance database (PVDB) summary to support PLLR.
- NDA 21951 for Absorica was first approved in the US on May 25, 2012.
- On August 17, 2018, Sun submitted a New Drug Application (NDA) 211913 for Absorica LD (low dose) via the 505b2 route with NDA 21951 as the reference listed drug (RLD). This submission included a literature search and PVDB summary to support PLLR. On May 2, 2019, Sun submitted revised labeling to comply with PLLR. DDDP consulted DPMH on June 10, 2019, to assist with the Pregnancy and Lactation subsections of labeling.
- In July 2019, DDDP determined that Absorica and Absorica LD would share a single label. DPMH notified DDDP that we would provide a single consult.

Current State of the Labeling for Absorica NDA 21951

Due to the length of the labeling this will be presented in Attachment A at the end of this document.

REVIEW

Nonclinical Experience

Since there is extensive human data on isotretinoin, the nonclinical data with regards to pregnancy is not included in labeling.

Review of Pharmacovigilance Database

Pregnancy outcomes for isotretinoin since the inception of the iPLEDGE program have been reviewed by the Office of Surveillance and Epidemiology (OSE). The reader is referred to OSE reviews from year 3.5 to year 12 (which includes 6 years of Absorica data) in DARRTS for details. A summary will be provided here of the cumulative data from inception to the year 12 review[1].

- The estimated pregnancy rate for Year 12 is calculated to be 0.09%.
- A total of 295,023 patients enrolled in iPLEDGE for the current reporting period. A total of 50% of new enrollees were females of reproductive potential (FRP). The total patient enrollment is 2,903,592 since program inception. Cumulatively through Year 12, 47% of patients have been females of reproductive potential (FRP), 3% females not of reproductive potential (FnRP) and 50% males. Cummulative through year 12 there have been 1,365,618 FRP enrolled.

[1] Review of the 6-Year Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Absorica (isotretinoin) and Year 12 for iPLEDGE (March 1, 2017 to February 28, 2018). Igor Cerny, Pharm.D. REMS Assessment Analyst, Division of Risk Management (DRISK). March 15, 2019. Darrts Reference ID#: 4404879.

A total of 175 iPLEDGE pregnancies (total excludes one false positive result) were reported during Year 12, of which 169 pregnancies 97%) were classified as isotretinoin-exposed. The following table describes the cummulative pregnancy outcomes for iPLEDGE pregnancies.

Table 1: Pregnancy Outcomes for iPLEDGE Pregnancies

Pregnancy Outcome	Year 10 (N =153)	Year 11 (N =183)	Year 12 (N =175)	Cumulative since Porgram Inception (N =1,957
Number of Outcomes	**154**	**183**	**175**	**1,960**
Elective Termination	67	80	72	947
Spontaneous Abortion	13	24	12	187
Live Birth	8	9	0	91
Ectopic Pregnancy	4	1	4	25
Still Continuing	0	0	25	25
Unknown	4	5	6	19
Missed Abortion	0	1	0	12
Still Birth	0	0	0	2
Lost to Follow-up[a]	**58**	**63**	**56**	**652**
Patient did not remain under health care provider's care	14	33	34	350
No response from patient	12	8	1	101
No pregnancy outcome	18	13	8	77
Patient refused to participate	5	4	7	60
No response from health care provider	6	2	3	41
No information provided	3	3	3	23
Health care provider left practice	0	0	0	0
Unknown	0	0	0	0
Duplicate case	0	0	0	0
Not pregnant/false positive	0	0	0	0

a Lost to follow-up includes cases where outcome is unknown and cases where outcome is known to have occurred but specifics surrounding outcome of pregnancy are unknown.

Source: OSE review Year 12[1], page 27/81.

Review of Literature

The applicant for NDA 21951 (Sun) submitted a 657-page summary and review of the literature for isotretinoin and human pregnancy-related issues based on a PubMed search of the published literature through May of 2018. An initial yield of > 1000 publications was narrowed down to

129 relevant publications which were submitted. See Table 3 in the applicant's submission[2] for details. Sun also submitted a 129 -page summary and review of the literature for isotretinoin and human pregnancy-related issues for NDA 211913 which includes identical information to that submitted under NDA 21951 (the first 124 pages). In both cases, the applicant concluded that isotretinoin is a potent teratogen and that no new information regarding its effect on pregnancy that requires inclusion in labeling has been found in the published literature.

DPMH performed a search of the published literature and agreed with the applicant's conclusion. There is ample human evidence that isotretinoin is a potent teratogen; this is captured in current labeling, and no new information that needs to be included in labeling has been found.

LACTATION

Nonclinical Experience

No animal data regarding lactation are available.

Review of Literature

No relevant literature regarding the use of isotretinoin in lactating women was identified by the applicant or by the DPMH reviewer.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

See this review, under "Current State of the Labeling for Absorica N21951"

Review of Literature

The applicant identified 19 relevant publications regarding isotretinoin and its effects on fertility. The majority of these publications were older and had been reviewed for previous versions of the labeling. The following publications regarding the effects of isotretinoin on ovarian reserve had not been previously assessed and the applicant proposes to include these results in the combined Absorica/Absorica LD label.

- Akturk[3] AS et al. (2014) described a study that was conducted to investigate possible effects of isotretinoin on ovarian reserve. For this, serum anti-Mullerian hormone (AMH) levels were measured at the beginning and at the end of isotretinoin treatment in 22 patients with acne and in 22 women without.

  The mean AMH level after treatment was statistically lower than the AMH level before treatment (p=0.012) in the patients' group. There was no significant difference between the mean AMH level at the end of treatment and that of the control group (p=0.20).

  The high level of pre-treatment AMH levels could be an evidence of hyperandrogenism in women with acne, even if they are not identified as having polycystic ovary syndrome (PCOS) or hyperandrogenism. The authors concluded that the decrease in AMH levels

[2] Published Clinical Literature Relevant to the Use of Isotretinoin During Pregnancy, Lactation and any Potential Effects on Fertility. NDA 21951. June 2018. Page 14/657.

[3] Aktürk AS et al (2014). The effects of isotretinoin on the ovarian reserve of females with acne. Gynecol Endocrinol; 30(1):30-3. PMID: 24256373

following exposure to isotretinoin may suggest that it has a detrimental effect on the ovaries.

- Ozturk[4] S et al (2015) investigated the effects of isotretinoin treatment on ovarian function in females with acne. Thirty-two female patients with severe acne were treated with oral isotretinoin 0.5- 2 mg/kg/d. The total cumulative dose for a full course was 120-135 mg/kg. The treatment duration ranged from 5 to 8 months. The serum follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels and antral follicle count (AFC) and ovarian volume (OV) were evaluated before and after treatment. After treatment, the mean FSH, LH, and E2 levels were significantly lower than before treatment. In addition, the mean AFC and OV decreased after treatment, although the difference was not significant. The authors concluded the results of this exploratory study did not demonstrate that oral isotretinoin had an impact in ovarian function. In contrast, isotretinoin affects levels of female hormones in patients with severe acne.
- Askoy[5] H et al. (2015) evaluated the impact of oral isotretinoin on ovarian reserve based on hormonal parameters, AMH, OV, and AFC in 82 women of reproductive age with acne who were treated with oral isotretinoin. The patients were evaluated for ovarian reserve prior to therapy and reevaluated 6 months after isotretinoin treatment with regard to hormonal parameters, AMH, OV, and AFC. The authors concluded that their study demonstrated that oral isotretinoin had a significant negative effect on ovarian reserve.
- Cinar[6] SL et al (2017) assess the long-term effects of isotretinoin on female fertility, the authors reevaluated 79 patients for AMH, OV, and AFC, FSH, LH, estradiol, free testosterone and total testosterone, twelve months after the end of systemic isotretinoin treatment.

  The authors reported that the changes in the mean AMH, OV and AFC were statistically significant between the sixth and eighteenth months (the end of systemic isotretinoin treatment and treatment-free 12 months). The mean AMH, OV and AFC values at the beginning and at the 18th month were statistically similar. There were no statistically significant changes in terms of FSH and LH, both at the end of the treatment and 12 months after the end of treatment. The change in the mean estradiol levels between the sixth month and 18th month was not significant. Both mean free and total testosterone levels increased significantly at the 18th month when compared with those at the sixth month (end of isotretinoin therapy). However, these increased values were still lower than the pretreatment values.

  It was concluded by the authors, that the deteriorative effects of systemic isotretinoin treatment on ovarian reserve, which can be accepted as an indicator of female fertility, diminish in time. The improvement in the ovarian reserve parameters twelve months after the end of therapy can be explained by the disappearance of the toxic effects of retinoic

[4] Öztürk S et al (2015). Evaluation of ovarian reserve and function in female patients treated with oral isotretinoin for severe acne: an exploratory study. Cutan Ocul Toxicol. 2015. Mar;34(1):21-4. PMID: 24678743.
[5] Aksoy H et al (2015). The effect of isotretinoin on ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with acne. Gynecol Obstet Invest. 2015;79(2):78-82. PMID: 25660129.
[6] Cinar SL et al, (2017). Long-term effect of systemic isotretinoin on female fertility. Cutan Ocul Toxicol. 2017 Jun;36(2):132-134. PMID: 27292185.

acid on the ovaries. Another explanation could be the diminishing of the mental depressive effects of the drug. The authors also hypothesized that the possible depressive effect of isotretinoin decreases with time and some of the hormonal parameters return to pretreatment levels after a treatment free period.

DISCUSSION AND CONCLUSIONS

DPMH recommends reformatting and rearranging much of the content of the Absorica and Absorica LD labeling in order to conform to the PLLR labeling requirements. At a future date, DPMH recommends that a REMS modification should be combined with revisions to the contraception recommendations (as per DPMH review by Dr. Leyla Sahin[7]).

Pregnancy

DPMH agrees with the sponsor's conclusion. There is ample human evidence that isotretinoin is a potent teratogen; this is captured in current labeling, and no new information that needs to be included in labeling regarding this topic has been found.

Lactation

No new information regarding the use of isotretinoin in lactating women was identified by the applicant or by the DPMH reviewer. No new information that needs to be included in labeling regarding this topic has been found.

Females and Males of Reproductive Potential

DPMH agrees with the sponsor that information regarding the effect of isotretinoin on the ovarian reserve should be added to labeling for Absorica and Absorica LD. Given the small size and other limitations, such as a lack of control group, this study is not definitive and these limitations will be noted in labeling.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 2, 4, 5, 7, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on July 1, 3, 5, 10, 2019. DPMH recommendations are below and reflect the discussions with DDDP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Absorica and Absorica LD (isotretinoin) Pregnancy and Lactation Labeling

See Labeling under Attachment B.

[7] DPMH Review of iPledge Risk Evaluation and Mitigation Strategy (REMS) Pregnancy Testing and contraception requirements for Absorica. NDA 21951. Leyla Sahin, MD. May 3, 2017. DARRTS Reference ID 4092695.

Attachment A

Current State of the Labeling for Absorica NDA 21951

- The most recently approved label for Absorica NDA 21951 is from August 31, 2018 and is in PLR hybrid format but not PLLR format. There is no current labeling for Absorica LD as it is a new NDA.
- There is a **boxed warning** for Birth Defects that notes a category X rating and states the following
    - ABSORICA must not be used by patients who are or may become pregnant. (5, 8.1, 8.6)
    - There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. (5.1, 8.1)
    - There are no accurate means of determining whether an exposed fetus has been affected. (5.1, 8.1)
    - Birth defects which have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion and premature births have been reported (8.1).
    - Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases, death has occurred with certain abnormalities previously noted (8.1).
    - If pregnancy does occur during the treatment of a patient who is taking ABSORICA, ABSORICA must be discontinued immediately and the patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling (8.1).
    - Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program called the iPLEDGE program. Prescribers, patients, pharmacies, and distributors must enroll in the program. (5.2)
- The **Dosage and Administration** Section states "Pregnancy Testing and Contraceptive measures must be followed prior to dosing ABSORICA" (8.6).
- There is a **Contraindication** to pregnancy (4.1, 8.1) that states the following:

    ABSORICA can cause fetal harm when administered to a pregnant patient. Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin in any amount and even for short periods of time. ABSORICA is contraindicated in patients who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued, and the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.
- **Warnings and Precautions** relevant to PLLR include

ABSORICA must not be used by patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time.

5.1 Embryofetal Toxicity

Teratogenicity

Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin *[see Use in Specific Populations (8.1)]*. Patients who can become pregnant must comply with the pregnancy testing and contraception requirements described in the iPLEDGE program *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6)]*. There are no accurate means of determining whether an exposed fetus has been affected.

5.2 iPLEDGE Program

Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program under a REMS called iPLEDGE. Under the ABSORICA REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program. ABSORICA must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE program. Only FDA approved isotretinoin products must be distributed, prescribed, dispensed, and used.

Required components of the iPLEDGE Program are:

- ABSORICA must only be prescribed by prescribers who are registered and activated with the iPLEDGE program and agree to comply with the REMS requirements described in the booklets entitled *Guide to Best Practices for the iPLEDGE Program*, *Prescriber Contraception Counseling Guide*, and *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin.*
- Patients who cannot become pregnant: To obtain ABSORICA, these patients must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *Guide to Isotretinoin for Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Patients who can become pregnant: ABSORICA is contraindicated in patients who are or may become pregnant *[see Contraindications (4.1)]*.
- Patients who are not pregnant but can become pregnant must understand the risks and benefits, comply with the REMS requirements described in the booklet entitled *Guide to Isotretinoin for Patients Who Can Get Pregnant* and *Birth Control Workbook* (including the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6), Patient Counseling Information (17)]*), and sign a Patient Information/Informed Consent form and Patient Information/Informed

Consent About Birth Defects form. Additionally, the patient must answer questions about the iPLEDGE program and pregnancy prevention monthly.

- Pharmacies that dispense ABSORICA must be registered and activated with iPLEDGE, must only dispense to patients who are authorized to receive ABSORICA, and agree to comply with the REMS requirements described in the booklet entitled *Pharmacist Guide*, specifically the "Key Information for Pharmacists" section including the following dispensing information:
  - Prescriptions must be obtained no later than the "Do Not Dispense To After" date, and if not obtained, then the RMA must be reversed in the iPLEDGE Program system and the product returned to inventory.
- Patients who can become pregnant must obtain the prescription within 7 days of the specimen collection for the pregnancy test; patients who cannot become pregnant must obtain the prescription within 30 days of the office visit.
- ABSORICA must only be dispensed in no more than a 30-day supply with a Medication Guide. Refills require a new prescription and a new authorization from the iPLEDGE system.
- Wholesalers and distributors that distribute ABSORICA must be registered with iPLEDGE and agree to comply with the REMS requirements.

If a pregnancy does occur during ABSORICA treatment, ABSORICA must be discontinued immediately. The patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or 1 month after ABSORICA therapy must be reported immediately to the FDA via the MedWatch telephone number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

Further information, including a list of qualified pharmacies, is available at www.ipledgeprogram.com or 1-866-495-0654.

5.3 Unacceptable Contraception
Micro-dosed Progesterone Preparations
Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during ABSORICA therapy.

- Under drug interactions, the labeling states

7 DRUG INTERACTIONS
7.6 Norethindrone/ethinyl estradiol
In a trial of 31 premenopausal female patients with severe recalcitrant nodular acne receiving Norethindrone/ethinyl estradiol as an oral contraceptive agent, isotretinoin at the recommended dose of 1 mg/kg/day, did not induce

clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

- Under **Section 8 USE IN SPECIFIC POPULATIONS**

  8.1 Pregnancy

  Pregnancy Category X *[see Contraindications (4), Warnings and Precautions (5.1)]*.

  Risk Summary

  ABSORICA is contraindicated during pregnancy because isotretinoin can cause fetal harm when administered to a pregnant patient. There is an increased risk of major congenital malformations, spontaneous abortions, and premature births following isotretinoin exposure during pregnancy in humans. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to a fetus.

  Clinical Considerations

  If pregnancy does occur during treatment of a patient who is taking ABSORICA, ABSORICA must be discontinued immediately and the patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

  Human Data

  Major congenital malformations that have been documented following isotretinoin exposure include: malformations of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. External malformations include: skull; ear (including anotia, micropinna, small or absent external auditory canals); eye (including microphthalmia); facial dysmorphia and cleft palate. Internal abnormalities include: CNS (including cerebral and cerebellar malformations, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular; thymus gland; parathyroid hormone deficiency. In some cases, death has occurred as a result of the malformations.

  Isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a patient who can become pregnant would be about one million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown and 20 years of postmarketing reports include four reports with isolated defects compatible with features of retinoid exposed fetuses, two of these reports were incomplete and two had other possible explanations for the defects observed.

Cases of IQ scores less than 85 with or without other abnormalities have been reported. An increased risk of spontaneous abortion and premature births have been documented with isotretinoin exposure during pregnancy.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ABSORICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.6 Patients of Reproductive Potential

All patients who can become pregnant must comply with the iPLEDGE program requirements *[see Warnings and Precautions (5.2)]*.

Pregnancy Testing

ABSORICA must only be prescribed to patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test. Patients who can become pregnant must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial ABSORICA prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for ABSORICA. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests must be at least 19 days.

- For patients with regular menstrual cycles, perform the second pregnancy test during the first 5 days of the menstrual period immediately preceding the beginning of ABSORICA therapy and after the patient has used 2 forms of contraception for 1 month.
- For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, perform the second pregnancy test immediately preceding the beginning of ABSORICA therapy and after the patient has used 2 forms of contraception for 1 month.

Each month of continued ABSORICA therapy, patients must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month, in a CLIA-certified laboratory, prior to the patient receiving each prescription. A pregnancy test must also be completed at the end of the entire course of isotretinoin therapy and 1 month after the discontinuation of isotretinoin.

Contraception

Patients who can become pregnant must use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence not having any sexual contact with a partner

which may result in pregnancy, or the patient has undergone a hysterectomy or bilateral oophorectomy or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of ABSORICA therapy, during ABSORICA therapy, and for 1 month after discontinuing ABSORICA therapy. Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during isotretinoin therapy *[see Warnings and Precautions (5.3)]*.

Effective forms of contraception include both primary and secondary forms of contraception:

Primary forms	Secondary forms
• Tubal sterilization • Male vasectomy • Intrauterine device • Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)	Barrier: • male latex condom with or without spermicide • diaphragm with spermicide • cervical cap with spermicide Other: • Vaginal sponge (contains spermicide)

Any birth control method can fail. There have been reports of pregnancy from patients who can become pregnant who have used combination oral contraceptives, as well as transdermal patch/ injectable/ implantable/ vaginal ring hormonal birth control products; these pregnancies occurred while taking isotretinoin. These reports are more frequent for patients who use only a single form of contraception. Therefore, it is critically important that patients who can become pregnant use 2 effective forms of contraception simultaneously.

Using 2 forms of contraception simultaneously substantially reduces the chances that a patient will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for isotretinoin. Although hormonal contraceptives are highly effective, prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort *[see Drug Interactions (7.4)]*.

If the patient has unprotected sexual contact with a partner that could result in pregnancy at any time 1 month before, during, or 1 month after therapy, the patient must:

a. Stop taking ABSORICA immediately, if on therapy
b. Have a pregnancy test at least 19 days after the last act of unprotected sexual contact with a partner which could result in pregnancy
c. Start using 2 forms of effective contraception simultaneously again

for 1 month before resuming ABSORICA therapy

d. Have a second pregnancy test after using 2 forms of effective contraception for 1 month as described above depending on whether the patient has regular menses or not.

If a pregnancy does occur during ABSORICA treatment, ABSORICA must be discontinued immediately. The patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or 1 month after ABSORICA therapy must be reported immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com) *[see Warnings and Precautions (5.2)]*.

- Under Section **13 NONCLINICAL TOXICOLOGY**

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for

appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen.

In trials of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

13.2 Animal Toxicology

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

- Under Section **17 PATIENT COUNSELING INFORMATION**

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Advise the patient that ABSORICA is only available through a restricted program Called iPLEDGE.

- As a component of the iPLEDGE program, prescribers must instruct patients to read the Medication Guide, the iPLEDGE program patient educational booklets, the iPLEDGE Program Birth Control Information Sheet and watch the video with the following videos — “Be Prepared, Be Protected” and “Be Aware: The Risk of Pregnancy While on Isotretinoin”. The video includes information about contraception, the most common reasons that contraception fails, the importance of using 2 forms of effective contraception when taking teratogenic drugs, and comprehensive information about types of potential birth defects which could occur if a patient who is pregnant takes ABSORICA at any time during pregnancy.
- Patients who cannot become pregnant must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *Guide to Isotretinoin for Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Patients who can become pregnant must be instructed that they must not be pregnant when ABSORICA therapy is initiated or plan to become pregnant while receiving ABSORICA therapy. Additionally, they must

use 2 forms of effective contraception simultaneously for 1 month before starting ABSORICA, while taking ABSORICA, and for 1 month after ABSORICA has been stopped, unless they commit to continuous abstinence from not having any sexual contact with a partner which could result in pregnancy. They should also sign a Patient Information/Informed Consent form and Patient Information/Informed Consent About Birth Defects (for patients who can get pregnant) form prior to beginning ABSORICA therapy. Patients who can become pregnant should be seen by their prescribers monthly and have a urine or serum pregnancy test, in a CLIA-certified laboratory, performed each month during treatment to confirm negative pregnancy status before another ABSORICA prescription is written. Additionally, a pregnancy test must be completed at the end of the entire course of ABSORICA therapy and 1 month after discontinuation of therapy.

- Advise the patient that isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a patient who can become pregnant would be about one million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown, 20 years of postmarketing reports include four with isolated defects compatible with features of retinoid exposed fetuses; however, two of these reports were incomplete and two had other possible explanations for the defects observed.

Attachment B-Proposed labeling

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LYNNE P YAO
09/03/2019 10:06:36 AM

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

PATIENT LABELING REVIEW

Date:	August 6, 2019
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ABSORICA LD (isotretinoin)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 211913
Applicant:	Sun Pharmaceuticals Industries LTD

1 INTRODUCTION

On August 17, 2018, Sun Pharmaceuticals Industries LTD submitted for the Agency's review a 505 (b)(2) New Drug Application (NDA) 211913 for ABSORICA LD (isotretinoin) capsules. The Reference Listed Drug (RLD) is ABSORICA (isotretinoin) capsules NDA 021951. The proposed indication is for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on July 18, 2019 and July 17, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ABSORICA LD (isotretinoin) capsules.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DDDP under separate cover.

2 MATERIAL REVIEWED

- Draft ABSORICA LD (isotretinoin) capsules MG received on August 17, 2018, and received by DMPP and OPDP on July 19, 2019.
- Draft ABSORICA LD (isotretinoin) capsules Prescribing Information (PI) received on August 17, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 19, 2019.
- Approved ABSORICA (isotretinoin) capsules NDA 021951 comparator labeling dated August 31, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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08/06/2019 02:29:43 PM

MORGAN A WALKER
08/06/2019 02:33:53 PM

LASHAWN M GRIFFITHS
08/06/2019 02:53:03 PM

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

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

Memorandum

Date: August 5, 2019

To: Roselyn Epps/Clinical Reviewer, M.D.
Division of Dermatology and Dental Products (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for ABSORICA LD™ (isotretinoin) capsules, for oral use

NDA: 211913

In response to DDDP's consult request dated July 16, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for ABSORICA LD™ (isotretinoin) capsules, for oral use (Absorica).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on July 19, 2019.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 19, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

Absorica LD Container/Carton Comments

1. OPDP notes that the following statement appears under the heading "**Mental problems and suicide**" on the wallet portion of all strengths of the carton/container labeling, "(b) (4) ." We are concerned that this statement has promotional tones and minimizes risk. It is not found in the PI and we recommend deletion from the labeling.
2. We note that the warning regarding the lack of interchangeability of other 20 mg isotretinoin products appears on the wallet label for Absorica LD 20 mg. OPDP recommends that it also be placed on the outer carton labeling to effectively communicate the warning.

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/s/

LAURIE J BUONACCORSI
08/05/2019 01:24:37 PM

M E M O R A N D U M

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

DATE: 2/22/2019

TO: Division of Dermatology and Dental Products
Office of Drug Evaluation IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211913

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the sites in September 2018 and January 2017, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs NON-RESPONSIVE .

The final classification for the inspections was No Action Indicated (NAI).

OSIS would like to note that an inspection was conducted at the Novum, Las Vegas site on January 23, 2019. The OSIS review will be completed on or before the end of March, 2019.

Therefore, based on the outcome of the previous inspections and the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services	11300 Richmond Avenue, Houston, TX
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV

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/s/

ANGEL S JOHNSON
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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:	January 25, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 211913
Product Name and Strength:	Absorica LD (isotretinoin) capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharmaceutical Industries Limited
FDA Received Date:	October 29, 2018
OSE RCM #:	2018-1793
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Absorica LD (isotretinoin) capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg, the Division of Dermatology and Dental Products (DDDP) requested that we review the proposed label and labeling for areas 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

Table 2 below includes the identified medication error issues with the submitted label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Sun Pharmaceutical Industries Limited (entire table to be conveyed to Applicant)

Container Labels			
1.	The format for the expiration date is not defined.	We are unable to determine if the format of your intended expiration date is such that it minimizes confusion and reduces the risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend 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. We recommend that a hyphen or a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).
2.	The (b) (4) color used on the carton labeling Absorica LD does not provide adequate differentiation when compared to the currently marketed Absorica products, given the color scheme and design of the carton labeling.	Lack of adequate differentiation may contribute to selection errors (wrong drug).	Revise the color scheme used to a distinct color to adequately differentiate it from the Absorica products. Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the carton labels as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling

			Design to Minimize Medication Errors, April 2013.
Carton Labeling			
1.	The (b) (4) color used on the carton labeling Absorica LD does not provide adequate differentiation when compared to the currently marketed Absorica products, given the color scheme and design of the carton labeling.	Lack of adequate differentiation may contribute to selection errors (wrong drug).	Revise the color scheme used to a distinct color to adequately differentiate it from the Absorica products. Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the carton labels as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
2.	The format for the expiration date is not defined.	We are unable to determine if the format of your intended expiration date is such that it minimizes confusion and reduces the risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend 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. We recommend that a hyphen or

			a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).

4 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the Sun Pharmaceutical Industries Limited so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Absorica LD that Sun Pharmaceutical Industries Limited submitted on October 29, 2018, and the listed drug.

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Absorica LD</th></tr>
<tr><td>Product Name</td><td>Absorica (NDA 021951)</td><td>Absorica LD (NDA 211913)</td></tr>
<tr><td>Initial Approval Date</td><td>May 25, 2012</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>isotretinoin</td><td>isotretinoin</td></tr>
<tr><td>Indication</td><td>treatment of severe recalcitrant nodular acne in patients 12 years of age and older</td><td>treatment of severe recalcitrant nodular acne in patients 12 years of age and older</td></tr>
<tr><td>Route of Administration</td><td>oral</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>capsules</td><td>capsules</td></tr>
<tr><td>Strength</td><td>10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg</td><td>8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg</td></tr>
<tr><td>Dose and Frequency</td><td>0.5 to 1 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2 mg/kg/day, as tolerated
<table>
<tr><th colspan="2">Body Weight</th><th colspan="3">Total Daily (mg)</th></tr>
<tr><th>Kilograms</th><th>Pounds</th><th>0.5 mg/kg</th><th>1 mg/kg</th><th>2 mg/kg</th></tr>
<tr><td>40</td><td>(b) (4)</td><td>20</td><td>40</td><td>80</td></tr>
<tr><td>50</td><td></td><td>25</td><td>50</td><td>100</td></tr>
<tr><td>60</td><td></td><td>30</td><td>60</td><td>120</td></tr>
<tr><td>70</td><td></td><td>35</td><td>70</td><td>140</td></tr>
<tr><td>80</td><td></td><td>40</td><td>80</td><td>160</td></tr>
<tr><td>90</td><td></td><td>45</td><td>90</td><td>180</td></tr>
<tr><td>100</td><td></td><td>50</td><td>100</td><td>200</td></tr>
</table></td><td>0.4 to 0.8 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 1.6 mg/kg/day of ABSORICA LD, as tolerated.
<table>
<tr><th colspan="2">Body Weight</th><th colspan="3">Total Daily (mg)</th></tr>
<tr><th>Kilograms</th><th>Pounds</th><th>0.4 mg/kg</th><th>0.8 mg/kg</th><th>1.6 mg/kg</th></tr>
<tr><td>40</td><td>88</td><td>16</td><td>32</td><td>64</td></tr>
<tr><td>50</td><td>110</td><td>20</td><td>40</td><td>80</td></tr>
<tr><td>60</td><td>132</td><td>24</td><td>48</td><td>96</td></tr>
<tr><td>70</td><td>154</td><td>28</td><td>56</td><td>112</td></tr>
<tr><td>80</td><td>176</td><td>32</td><td>64</td><td>128</td></tr>
<tr><td>90</td><td>198</td><td>36</td><td>72</td><td>144</td></tr>
<tr><td>100</td><td>220</td><td>40</td><td>80</td><td>160</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td></td><td>The below table represents the comparison of strengths between ABSORICA LD and ABSORICA and other generic products available in the market.<table><tr><th>ABSORICA (strengths in mg)/ and other generic products available</th><th>ABSORICA LD (strengths in mg)</th></tr><tr><td>40 mg</td><td>32 mg</td></tr><tr><td>35 mg</td><td>28 mg</td></tr><tr><td>30 mg</td><td>24 mg</td></tr><tr><td>25 mg</td><td>20 mg</td></tr><tr><td>20 mg</td><td>16 mg</td></tr><tr><td>10 mg</td><td>8 mg</td></tr></table></td></tr>
<tr><td>How Supplied</td><td>Box of 30 capsules (3 x 10 Prescription Packs)</td><td>Box of 30 capsules (3 x 10 Prescription Packs)</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from light.</td><td>Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. Protect from light.</td></tr>
<tr><td>Container Closure</td><td>Carton containing 3 wallet cards</td><td>Carton containing 3 wallet cards</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS – N/A

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APPENDIX C. ISMP NEWSLETTERS – N/A

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APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

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APPENDIX E. OTHER – N/A

APPEARS THIS WAY ON ORIGINAL

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,[a] along with postmarket medication error data, we reviewed the following Isotretinoin (NDA 211913) labels and labeling submitted by Sun Pharmaceutical Industries Limited on October 29, 2018.

- Container labels (Wallet) received on October 29, 2018
- Carton labeling received on October 29, 2018
- Medication Guide (Image not shown) received on October 29, 2018
- Prescribing Information (Image not shown) received on October 29, 2018

F.2 Label and Labeling Images

Container labels (Wallet)

(b) (4)

[redacted]

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

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