

## Appendix S1

### Eligibility criteria for the fed bioequivalence and food-effect study

#### Inclusion criteria

1. Male and female participants 18 years of age or older, body mass index (BMI) 18–30 kg/m<sup>2</sup>, inclusive. BMI was calculated using Novum Pharmaceutical Research Services Standard Operating Procedures.
2. Female participants had to be of non-childbearing potential, defined as:
  - Naturally postmenopausal (no menses) for at least 2 years before initial dosing with a documented follicle-stimulating hormone level  $\geq 40$  mIU/ml at screening OR
  - Surgically postmenopausal/sterile (e.g. bilateral oophorectomy, tubal ligation, or hysterectomy), with the procedure performed at least 6 months before initial dosing.
3. If male, the participant agreed to use a reliable method of contraception throughout the duration of the study. Examples of acceptable methods of contraception included a double-barrier method of contraception (e.g. condom with spermicide). Other forms of contraception were acceptable, at the discretion of the investigator.
4. Good health as determined by a lack of clinically significant abnormalities in health assessments performed at screening.
5. Signed and dated informed consent form, which met all criteria of current Food and Drug Administration (FDA) regulations and contains warnings about the potential risks associated with isotretinoin.
6. Participant provided with and able to read the Medication Guide for the Orange Book RS, ABSORICA<sup>®</sup> (isotretinoin) capsules, 40 mg (Ranbaxy Laboratories Inc., Princeton, NJ, USA).

#### Exclusion criteria

1. Female participants of childbearing potential or who were pregnant, lactating, breastfeeding, or likely to become pregnant during the study.
2. History of allergy or sensitivity to isotretinoin, other retinoids, or vitamin A, or history of any drug hypersensitivity or intolerance that, in the opinion of the investigator, would compromise the safety of the participant or the study.
3. Significant history (personal or family) or current evidence of chronic infectious disease, system disorders or organ dysfunction, especially cardiovascular disorders (e.g. hypertension), asthma, diabetes, bone loss (osteoporosis) or weak bones, anorexia nervosa, hepatic, or renal disorders.
4. Clinically significant history or presence of gastrointestinal disease, inflammatory bowel disease, or history of malabsorption within the last year, as determined by the investigator.
5. History (personal or family) of psychiatric disorders (e.g. depression, psychosis, suicidal thoughts) occurring within the last 2 years that required the participant (or family member) to be hospitalized or treated with medication.
6. Presence of a medical condition requiring regular treatment with prescription drugs.
7. Use of systemic or topical corticosteroids, tetracycline antibiotics, Dilantin<sup>®</sup> (phenytoin), or St John's wort within 30 days before initial dosing.
8. Receipt of any drug as part of a research study within 30 days before initial dosing.
9. Drug or alcohol addiction that required treatment during the previous 12 months.
10. History of excessive alcohol consumption (on average more

- than 14 units of alcohol/week) during the previous 12 months.
11. Donation or significant loss of whole blood (480 ml or more) within 30 days or plasma within 14 days before initial dosing.
12. Positive test for HIV, hepatitis B surface antigen, or hepatitis C antibody.
13. Positive test results for drugs of abuse at screening.
14. If female, had a positive serum pregnancy test at screening.
15. If male, unwilling or unable to comply with the protocol's contraceptive requirements to ensure full commitment to pregnancy prevention.

### Eligibility criteria for the fasting study

#### Inclusion criteria

1. Male participants 18 years of age or older, body mass index (BMI) of 18–30 kg/m<sup>2</sup>, inclusive. BMI was calculated using Novum Pharmaceutical Research Services Standard Operating Procedures.
2. The participant, even if they have had a vasectomy, agreed to use a reliable method of contraception throughout the duration of the study and for at least 30 days after the last dose of study drug in this study and agreed to report to the clinic if their female partner became pregnant during this timeframe. Examples of acceptable methods of contraception included a double-barrier method of contraception (e.g. condom with spermicide). Other forms of contraception were acceptable, at the discretion of the investigator.
3. The participant agreed to not donate sperm throughout the duration of the study and for at least 30 days after the last dose of study drug in this study.
4. The participant agreed to not donate blood or plasma until at least one month after the last blood sample in this study.
5. Good health as determined by a lack of clinically significant abnormalities in health assessments performed at screening.
6. Signed and dated informed consent form, which meets all criteria of current FDA regulations and contains warnings about the potential risks associated with isotretinoin.
7. Participants were advised that isotretinoin is found in the semen of male participants taking isotretinoin, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. Although the no-effect limit for birth defects due to isotretinoin is unknown, 20 years of post-marketing reports include 4 with isolated defects compatible with the birth defects associated with isotretinoin; however, 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.
8. Participant provided with and able to read the Medication Guide for ABSORICA<sup>®</sup> (isotretinoin) capsules, 40 mg (Ranbaxy Laboratories Inc., Princeton, NJ, USA).

#### Exclusion criteria

1. Female individual.
2. History of allergy or sensitivity to isotretinoin, other retinoids, or vitamin A, or history of any drug hypersensitivity or intolerance that, in the opinion of the investigator, would compromise the safety of the participant or the study.
3. Significant history (personal) or current evidence of chronic infectious disease, system disorders, or organ dysfunction, especially cardiovascular disorders (e.g. hypertension), asthma, diabetes, lipid metabolism disorder, bone loss (osteoporosis), osteomalacia or weak bones, anorexia nervosa, hepatic, or renal disorders.
4. Clinically significant history or presence of gastrointestinal disease, inflammatory bowel disease, or history of malabsorption within the last year, as determined by the investigator.

5. History (personal or family) of psychiatric disorders (e.g. depression, psychosis, suicidal thoughts) occurring within the last 2 years that required the participant (or family member) to be hospitalized or treated with medication.
6. Presence of a medical condition requiring regular treatment with prescription drugs.
7. Use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days before initial dosing.
8. Use of systemic or topical corticosteroids, tetracyclines, Dilantin® (phenytoin), or St John's wort within 30 days before initial dosing.
9. Receipt of any drug as part of a research study within 30 days before initial dosing.
10. Drug or alcohol addiction requiring treatment during the previous 12 months.
11. History of excessive alcohol consumption (on average more than 14 units of alcohol/week) during the previous 12 months.
12. Donation or significant loss of whole blood (480 ml or more) within 30 days or plasma within 14 days before initial dosing.
13. Positive test results for HIV, hepatitis B surface antigen, or hepatitis C antibody.
14. Positive test results for drugs of abuse at screening.
15. Unwilling or unable to comply with the protocol's contraceptive requirements to ensure full commitment to prevention of pregnancy.