PLLR: Subsection 8.3 Females and Males of Reproductive Potential

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Subsection 8.3 Females and Males of Reproductive Potential

- Moves recommendations for pregnancy testing and contraception information from subsection 8.1 Pregnancy
- Moves human infertility statements and considerations from Section13 Nonclinical Toxicology
  - Animal study details remain in 13.1 Carcinogenicity, Genotoxicity and Fertility and 13.2 Animal Toxicology

Subsection 8.3 Is Optional

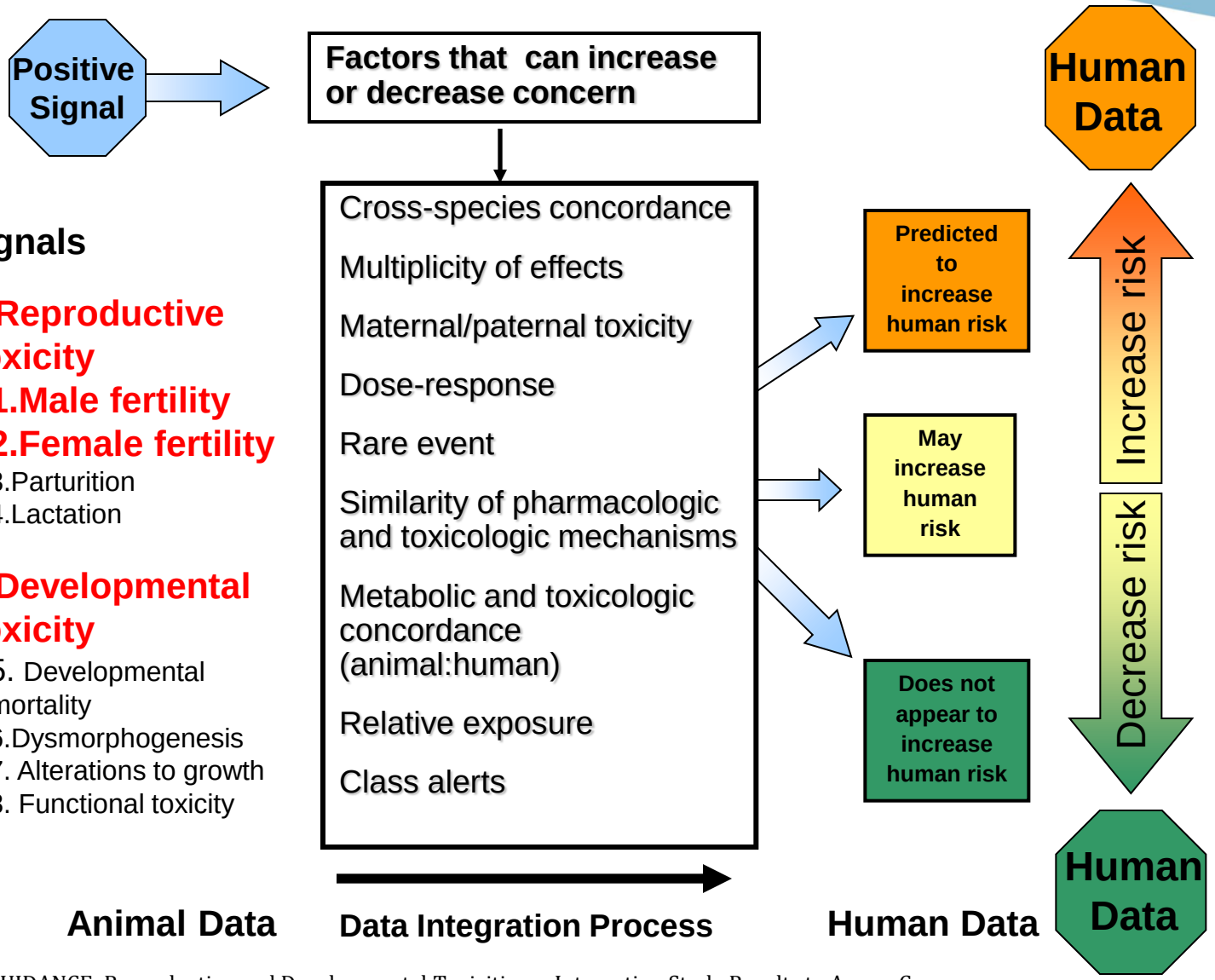
It should only be used when there is a need to communicate information regarding the following

- Adverse effects on fertility
- Provide information on
  - Contraception – type, duration, etc.
  - Pregnancy Testing
  - Breast Feeding

Step 1: Assessing Reproductive Risk

- Review of all nonclinical and clinical studies carried out to assess potential effects on reproduction and fetal development
- Perform a comparative evaluation of
  - Pharmacodynamic effects
  - Animal and human metabolic and disposition data
  - Animal and human toxicologic effects
  - Comparison of exposures in nonclinical studies relative to the highest proposed clinical exposure of the therapeutic

Step 2: Integration of Reproductive & Developmental Toxicities*



*CDER GUIDANCE; Reproductive and Developmental Toxicities —Integrating Study Results to Assess Concerns.

Step 2: Assess Need for Fetal Exposure Mitigation Strategies

Communicate data relevant for pregnancy prevention and planning

- Pregnancy testing
- Contraception (females and males)

Pregnancy Testing

Pregnancy testing should be recommended prior to prescribing drugs which are contraindicated or carry a warning and precaution statement (Former Category X and D pharmaceuticals)

Example: ERIVEDGE

ERIVEDGE can result in embryo-fetal death or severe birth defects. [see *Boxed Warning, Warnings and Precautions (5.1), Use in Specific Populations (8.1)*].

Female patients

- Determine pregnancy status within 7 days prior to initiation of treatment in females of reproductive potential. For females with a negative pregnancy test, initiate a highly effective form of contraception (failure rate of less than 1%) prior to the first dose.

Contraception

If contraception is recommended comment on duration and type (if relevant)

- Duration
  - Only needed during treatment
  - Duration (X half lives) following treatment for long acting drugs
- Type: hormonal, nonhormonal, barrier
  - Concomitant Use of CYP 3A4 Inducers

Example: CYTOXAN

Contraception: Pregnancy should be avoided during treatment with cyclophosphamide because of the risk of fetal harm *[see Use in Specific Populations (8.1)].*

Female patients of reproductive potential should **use highly effective contraception during and for up to 1 year** after completion of treatment.

Male patients who are sexually active with female partners who are or may become pregnant should **use a condom during and for at least 4 months after treatment**.

Example: ERIVEDGE

Contraception

Male patients

Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse with female partners while being treated with ERIVEDGE capsule and for 2 months after the last dose to avoid exposing an embryo or fetus to vismodegib.

Importance of Drug Interactions with Hormonal Contraceptives

Efficacy or safety drugs, including hormonal contraceptives may be affected due to drug-drug interactions.

- Changes in COC exposure:
  - ⇓ Exposure – Risk of Pregnancy
  - ⇑ Exposure – Risk of Cardiovascular Events

Example: TAFINLAR

Contraception: *Females*

Advise female patients of reproductive potential to **use highly effective contraception during treatment and for 4 weeks after treatment**. Counsel patients to **use a non-hormonal** method of contraception since **TAFINLAR can render hormonal contraceptives ineffective**. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.7), Drug Interactions (7.1), Use in Specific Populations (8.1)]*.

Example: JUXTAPID

Contraception

Females of reproductive potential should use effective contraception during JUXTAPID therapy. **The recommended maximum dosage of JUXTAPID is 30 mg daily with concomitant use of oral contraceptives, since oral contraceptives are weak CYP3A4 inhibitors *[see Drug Interactions (7.2)].* Hormone absorption from oral contraceptives may be incomplete if vomiting or diarrhea occurs while taking JUXTAPID, warranting the use of additional contraceptive methods *[see Warnings and Precautions (5.5)]*.**

Example: RIFADIN

Patients should be advised that the reliability of oral or other systemic hormonal contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Example: SUSTIVA

Contraception

- **Females** of reproductive potential should use effective contraception **during treatment** with SUSTIVA and for **12 weeks after discontinuing SUSTIVA** due to the long half-life of efavirenz.
- **Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness [*see Drug Interactions (7.1)*].**

INFERTILITY

Important Factors Regarding Fertility

The following information should be included when known:

- Complete vs. Partial
- Permanent vs. Temporary

Example: CYTOXAN

Infertility

Females **Amenorrhea, transient or permanent**, associated with decreased estrogen and increased gonadotropin secretion develops in a proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. The **risk of premature menopause** with cyclophosphamide increases with age. **Oligomenorrhea** has also been reported in association with cyclophosphamide treatment.

Animal data suggest an **increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases. The exact duration of follicular development in humans is not known, but may be longer than 12 months *[see Nonclinical Toxicology (13.1)]*.**

Males Men treated with cyclophosphamide may develop **oligospermia or azoospermia** .....

Example: TAFINLAR

Infertility: *Males*

Effects on spermatogenesis have been observed in animals. Advise male patients of the potential **risk for impaired spermatogenesis**, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR *[see Nonclinical Toxicology (13.1)].*

Example: BEXXAR

Infertility: The BEXXAR therapeutic regimen results in radiation exposure of the ovaries and testes. Based on published studies examining patients treated with I-131, the BEXXAR therapeutic regimen may cause **transient ovarian or testicular dysfunction**. Radiation effects **may persist for up to 12 months following treatment**.

TYING EVERTHING TOGETHER

Example: TAFINLAR

TAFINLAR

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------INDICATIONS AND USAGE ----------

TAFINLAR is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-app

----------WARNINGS AND PRECAUTIONS----------

- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus. TAFINLAR may render hormonal contraceptives less effective and an alternative method of contraception should be used. (5.7, 8.1)

----------USE IN SPECIFIC POPULATIONS ----------

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Advise female patients to use highly effective contraception during treatment and for 4 weeks following discontinuation of treatment. Advise male patients of potential risk for impaired spermatogenesis. (8.6) roved test. (1, 2.1)

TAFINLAR

5 WARNINGS AND PRECAUTIONS

5.7 Embryofetal Toxicity

Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception during treatment and for 4 weeks after treatment since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Drug Interactions (7.2), Use in Specific Populations (8.6)].*

TAFINLAR

7.2 Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate) *[see Clinical Pharmacology (12.3)]*. Monitor international normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of TAFINLAR with other substrates of these enzymes, including dexamethasone or **hormonal contraceptives, can result in decreased concentrations and loss of efficacy** *[see Use in Specific Populations (8.1, 8.6)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

TAFINLAR

8.1 Pregnancy

~~Pregnancy Category D~~

Risk Summary: Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses 3 times greater than the human exposure at the recommended clinical dose of 150 mg twice daily based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings* 189 *and Precautions (5.7)]*.

Animal Data: In a combined female fertility and embryofetal development study in rats, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately 3 times the human exposure at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater, (equivalent to the human exposure at the recommended dose based on AUC) rats demonstrated delays in skeletal development and reduced fetal body weight.

TAFINLAR

8.~~63~~ Females and Males of Reproductive Potential

Contraception: *Females*

Advise female patients of reproductive potential to use highly effective contraception during treatment and for 4 weeks after treatment. Counsel patients to use a non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.7), Drug Interactions (7.1), Use in Specific Populations (8.1)]*.

Infertility: *Males*

Effects on spermatogenesis have been observed in animals. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR *[see Nonclinical Toxicology (13.1)].*

TAFINLAR

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryofetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended dose based on AUC).

Male fertility studies with dabrafenib have not been conducted; however, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to and three times the human exposure at the recommended dose based on AUC, respectively.