PLLR: Subsection 8.3
Females and Males of Reproductive Potential

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Based on a presentation given by Linda Reid (FDA) at the previous HESI PLLR workshop

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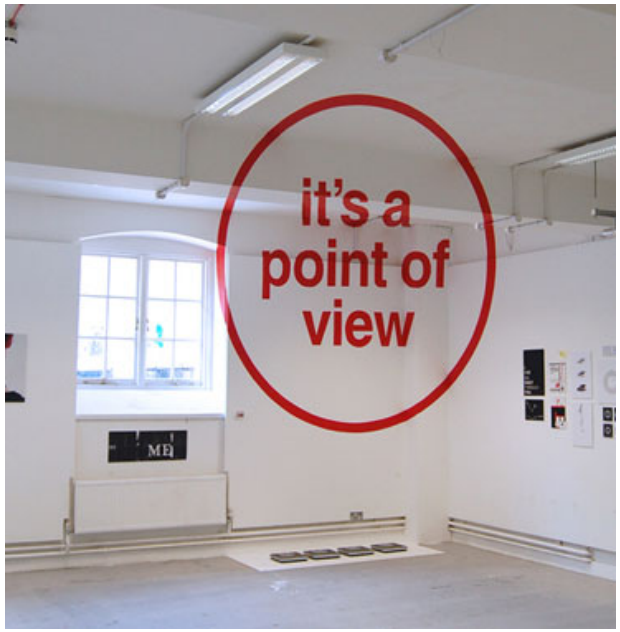
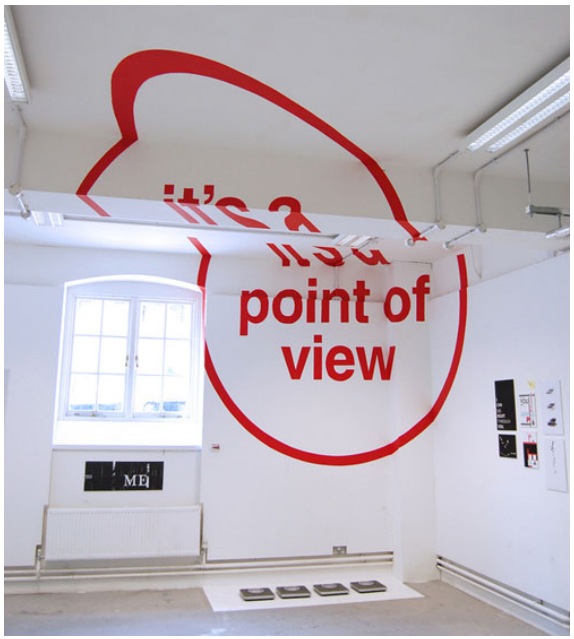




Anamorphic typographic installation by graphic design student Joseph Egan of the Chelsea College of Art & Design

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:
    - 13.1Carcinogenicity, Genotoxicity and Fertility
    - 13.2 Animal Toxicology

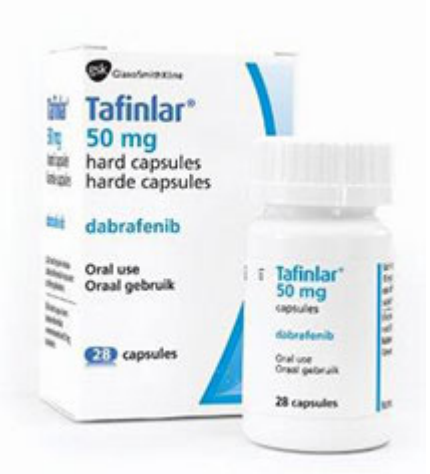
Subsection 8.3 Is Optional

- Only needed to communicate the following:
  - Adverse effects on fertility
  - Information on
    - Pregnancy testing
    - Contraception – type, duration, etc.
    - Fertility

Fertility: Important factors

- Male, female or both?
- Partial or complete?
- Permanent or transitory
  - Duration after stopping treatment

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)]*.

TAFINLAR

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

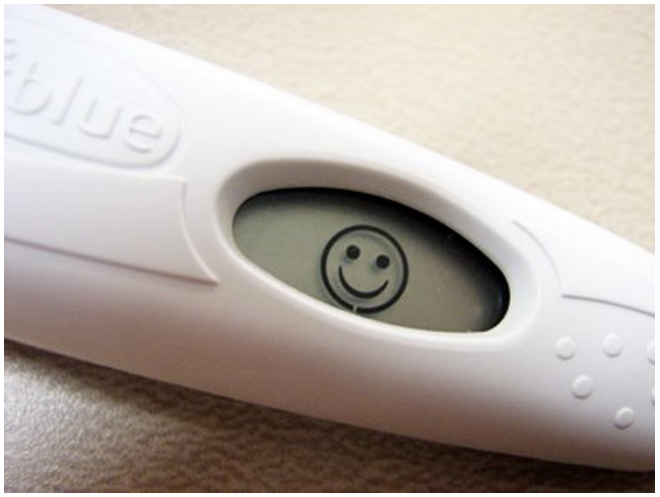
In a **combined female fertility and embryofetal development study** in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant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

Permanent or transitory?

Time for recovery?

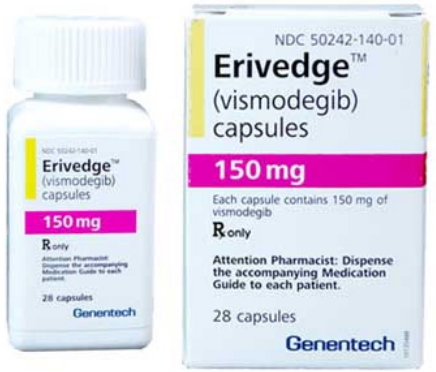
Pregnancy Testing



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)*].

Females

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

- 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,
    - Condom

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)].*

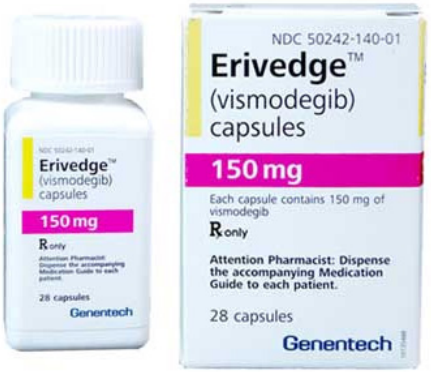
Female patients of reproductive potential should **use effective contraception during and for up to 1 year** after completion of treatment.

- Duration of follicular development

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**.

- Genetic toxicity, transmission in semen??

Example: ERIVEDGE

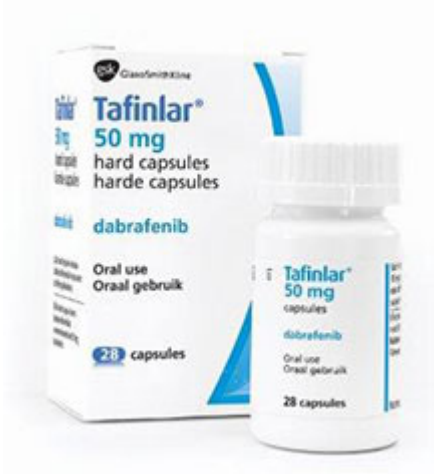


Contraception

Male patients

Vismodegib is present in semen [see Clinical Pharmacology (12.3)]. **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.

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**. *[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)]*.

Summary

- Section 8.3 is optional.
- It includes recommendations for:
  - Pregnancy testing and/or contraception in case of a warning or precaution statement for pregnancy
  - Risk of effects on fertility
  - Drug interactions with contraceptives.
- It does not include animal data
  - (cross referenced to sections 13.1 and/or 13.2).
- All recommendations must be coherent with identified risk.

Thanks for your attention

(It will all be over soon)