

Sustainability of estradiol drug concentrations in cut matrix patches; a study of different brands with potential use for pubertal induction

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Disclosure statement: The authors declare no financial conflict of interest. Pfizer has financially sponsored this research with an unrestricted grant. No products of Pfizer were involved in this study.

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Background: Transdermal estradiol (E₂) patches are primarily designed for adult women. No patches are labelled for children, i.e. pubertal induction in hypogonadal girls. Low doses for children can be achieved by cutting a matrix patch into smaller portions. However, the manufacturers do not guarantee stability or utility of cut E₂ patches.

Objective: To test if one month of storage in room temperature (+21C) or in "hot climate" (+35C) influence the drug amount of E₂ in cut matrix patches from four different manufacturers.

Conclusions

- As long as E₂ patches for children are not available, cut portions of the E₂ patches Oesclim[®], Estraderm MX[®] and System[®] can be used to induce puberty in hypogonadal girls.
- Unused patch fractions may be stored in their packaging for at least 1 month at +21C and even at +35C if needed.
- The Estradot[®] patch was too small to properly cut into small portions and not stable in hot climate.

Results

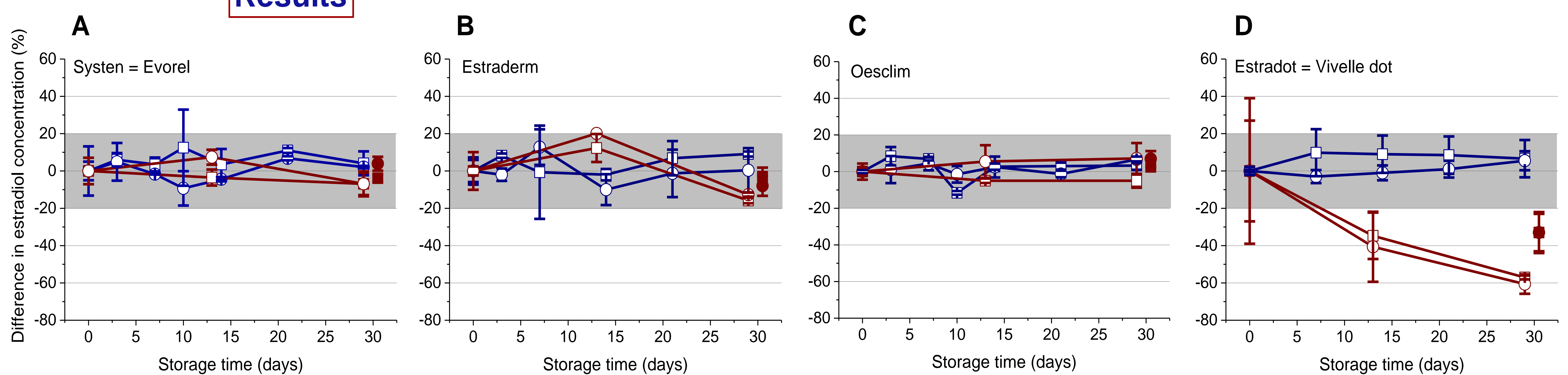


Figure 1. Evaluation of stability of four different E₂ matrix patches. Results are presented as mean difference in E₂ drug amount \pm SD compared to an intact patch that have been stored sealed at +21C until cut. The entire experiment was done in duplicates. $\pm 20\%$ was considered as acceptable.

Results: Storage in +21C or +35C up to 1 month did not affect the E₂ drug amount in System[®], Estraderm MX[®] and Oesclim[®] patches (Fig.1A-C). E₂ in Estradot[®] patch (Fig.1D) however, was not affected by storage in +21C, but in +35C E₂ decreased with 33% ($\pm 11\%$) in sealed patches and 61% ($\pm 5\%$) in cut patches, during 1 month storage. Storage in plastic bags gave similar results as storage without.

Patches were cut in parts and stored for up to 1 month either at +21C

- in its original sachet
- in its sachet covered with a small plastic bag
- in its original sachet
- in its sachet covered with a small plastic bag

Table 1. Description of four tested E₂ matrix patches

Brand name	System [®] (=Evorel [®])	Estraderm MX [®]	Oesclim [®] (=Esclim [®] , Esclima [®])	Estradot [®] (=Vivelle dot [®])
Manufacturer	Janssen-Cilag International	Merus Labs	Mylan Technologies	Novartis
Dose	50 µg per 24 hours.	50 µg per 24 hours.	25 µg per 24 hours	50 µg per 24 hours.
Amount E ₂ (mg)	3.2	1.5	5	0.78
Shape and color	A square-shaped, transparent, with rounded corners	Square-shaped, transparent with rounded corners	A beige rectangular foam mounting with rounded corners	Rectangular, transparent, with rounded corners
Patch area (cm ²)	16	22	11	5
Recommended storage conditions	In its protective sachet below +25C	In its protective sachet below +25C	In its protective sachet below +25C	In its protective sachet below +30C. Do not store Estradot [®] in refrigerator. Keep from freezing.

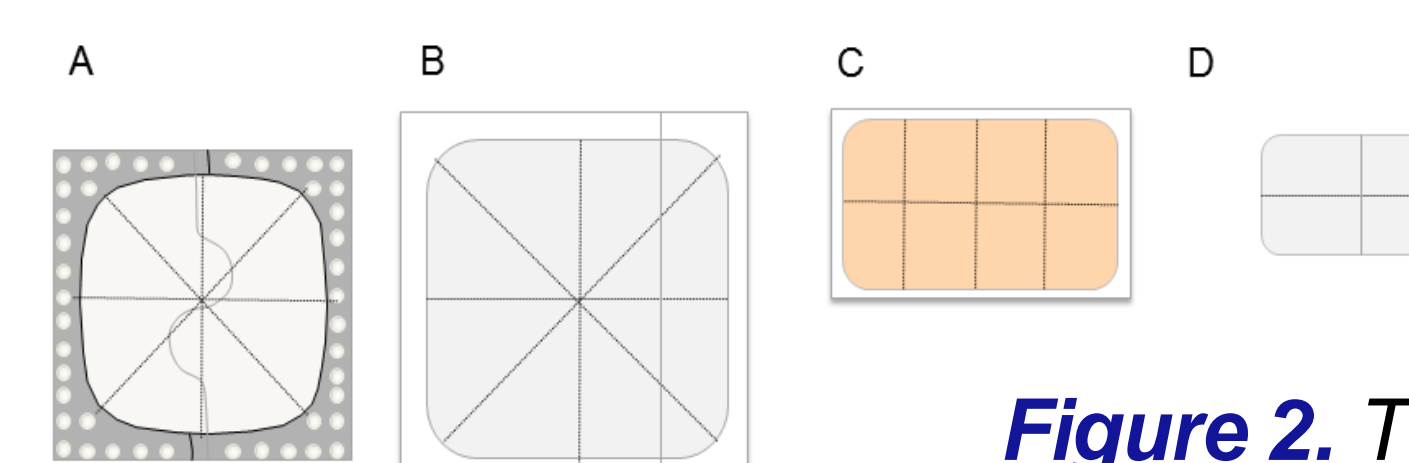


Figure 2. The dotted lines depict how the patches were cut.

Method: The System[®] (Fig.2A), Estraderm[®] (Fig.2B) and Oesclim[®] (Fig.2C) patches were cut into eight parts while Estradot[®] (Fig.2D) was cut into two parts. Patch portions were put back into respective sachet and sealed by hand. Half of the sachets were put in plastic bags and sealed. The patches were stored at room temperature (+21C) or in "hot climate" (+35C) in heating cabinet for up to 1 month.

The E₂ drug was extracted from the patch in a solution of ethyl acetate n-hexane and thereafter serially diluted. E₂ concentrations were determined by a validated RIA.

ESPE 2018, Athens, Greece