Risks associated with systemic exposure to [invented name; to be inserted nationally]

Dear Healthcare Professional,

<Marketing authorization holder> in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **Treatment with [invented name; to be inserted nationally] (containing estradiol 100 micrograms/g of cream) should be limited to one single period of up to 4 weeks due to the absence of long-term safety data;**
- **Pharmacokinetic data on 100 micrograms/g estradiol-containing products for intravaginal use show substantial systemic exposure to estradiol, which is higher than the normal postmenopausal range;**
- **Systemic exposure might be associated with risks known to be related to oral and transdermal HRT products;**
- **[invented name; to be inserted nationally] should not be used in patients who are treated with oral or transdermal HRT products.**

Background on the safety concern

[Invented name; to be inserted nationally] (containing estradiol 100 micrograms/g cream or emulsion) is indicated for relief of symptoms of vaginal atrophy due to estrogen deficiency in postmenopausal women.

Systemic levels of estradiol (up to five times above the upper limit of the reference postmenopausal estradiol serum levels of 10-20 pg/mL) after intravaginal administration of topical products containing estradiol 100 micrograms/g cream were observed in pharmacokinetic studies when dosed as per approved product information. Therefore, these products should be seen as high-strength products and might be associated with risks related to systemic exposure such as endometrial hyperplasia/carcinoma, breast and ovarian cancer and thromboembolic events.

Available clinical trial data are limited to treatment duration of 4 weeks only. Safety data on prolonged treatment as well as repeated treatment courses are not available. Given that systemic exposure occurs, [invented name; to be inserted nationally] should only be used for a single treatment period up to 4 weeks and vigilance is required for possible systemic effects. If symptoms of vaginal atrophy persist beyond 4 weeks, other treatment options should be considered.

In reported adverse drug reactions to topical high concentrated estradiol from EU Member States the concomitant use of systemic HRT was described quite frequently. Due to the significant systemic

exposure, [invented name; to be inserted nationally] should not be used in patients who are treated with systemic HRT.

The product information of [invented name; to be inserted nationally] will reflect risks associated with systemic exposure and restriction in duration of use. To minimize the risk of prolonged use due to the inherent chronic character of the vaginal atrophy and to ensure patients adherence to the recommended duration of use, only a 25 g package size of the product which represents one 4-week treatment cycle, will be available on the market.

Call for reporting

Any suspected adverse events should be reported to {Insert details of the national spontaneous reporting system e.g. name, postal address, fax number, website}

{Insert details (e.g. name, postal address, fax number, website address) on how to access to the national spontaneous reporting system}

Company contact point

{Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address}

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Medicinal products containing estradiol 0.01%w/w for topical use (cream/emulsion)
Marketing authorisation holder(s)	Dr. August Wolff GmbH & Co. KG Arzneimittel Pharmazeutische Fabrik Montavit Ges.M.B.H
Safety concern and purpose of the communication	Risks associated to systemic exposure with [invented name; to be inserted nationally]
DHPC recipients	Gynaecologists, General Practitioners, other healthcare professionals in line with national requirements
Member States where the DHPC will be distributed	Austria, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Latvia, Lithuania, Hungary, Slovakia.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	16 January 2020
DHPC and communication plan (in English) agreed by CMDh	30 January 2020
Submission of translated DHPCs to the national competent authorities for review	6 February 2020
Agreement of translations by national competent authorities	13 February 2020
Dissemination of DHPC	20 February 2020