

English wording to be implemented

SmPC

The texts of the 3rd revision of the Core SPC for HRT products, as published on the CMD(h) website, should be included in the SmPC. Where a statement in the Core SPC for HRT products applies equally to HRT and tibolone this should be made clear by replacing 'HRT' with 'HRT or tibolone' in the tibolone SmPC.

In addition to the texts of the 3rd revision of the Core SPC for HRT products, the following wordings have to be added:

Section 4.4

Under subheading 'Ovarian cancer'

In the Million Women Study it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT

Under subheading 'Venous thromboembolism'

In an epidemiological study using a UK database, the risk of VTE in association with tibolone was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of tibolone and a small increase in risk compared with non-use cannot be excluded.

Under subheading 'Coronary artery disease (CAD)'

In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Section 4.8

Under 'Breast cancer risk'

In Table 2: Million women study – estimated additional risk of breast cancer after 5 years' use

| <i>Age range (years)</i> | <i>Additional cases per 1000 never-users of HRT over a 5 year period*2</i> | <i>Risk ratio & 95%CI#</i> | <i>Additional cases per 1000 HRT users over 5 years (95%CI)</i> |
|---------------------------------|--|--------------------------------|---|
| <i>Estrogen only HRT</i> | | | |
| <i>50-65</i> | <i>9-12</i> | <i>1.2</i> | <i>1-2 (0-3)</i> |

| | | | |
|---|------|-----|---------|
| Combined estrogen-progestagen | | | |
| 50-65 | 9-12 | 1.7 | 6 (5-7) |
| Tibolone | | | |
| 50-65 | 9-12 | 1.3 | 3 (0-6) |
| <i>#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use.</i> | | | |

Under 'Ovarian cancer'

Long term use of estrogen-only and combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users. This study showed that the relative risk for ovarian cancer with tibolone was similar to the risk with other types of HRT.

Under 'Risk of coronary artery disease'

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4). There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT.

PL

The texts of the 3rd revision of the Core PL for HRT products, as published on the CMD(h) website, should be included in the PIL. Where a statement in the Core PL for HRT products applies equally to HRT and tibolone this should be made clear by replacing 'HRT' with 'HRT or tibolone' in the tibolone PIL.

In addition to the texts of the 3rd revision of the Core PL for HRT products, the following wordings have to be added:

PIL Section 2:

Under subheading 'Breast cancer', 'Compare' section

Women taking Livial have a lower risk than women using combined HRT and a comparable risk with estrogen-only HRT.

Under subheading 'Ovarian cancer', 'Compare' section

With use of Livial, the increased risk of ovarian cancer is similar to other types of HRT

Under subheading 'Blood clots in a vein (thrombosis)', 'Compare' section

With use of Livial, the increased risk of getting a blood clot in a vein is lower than with other types of HRT.

Under subheading 'Heart disease (heart attack)'

There is no evidence that HRT will prevent a heart attack.

Under subheading 'Stroke'

Compare

Looking at women in their 50s who are not taking Livial - on average, over a 5-year period, 3 in 1000 would be expected to have a stroke. For women in their 50s who are taking Livial, the figure would be 7 in 1000 (i.e. an extra 4 cases).

Looking at women in their 60s who are not taking Livial - on average, over a 5-year period, 11 in 1000 would be expected to have a stroke. For women in their 60s who are taking Livial, the figure would be 24 in 1000 (i.e. an extra 13 cases).

Dansk ordlyd, der skal implementeres

SmPC

Teksten fra tredje revision af core SPC for HRT produkter, som publiceret på CMD(h)s hjemmeside, skal implementeres i SmPC'et. Hvis udsagn i core SPC for HRT produkter henfører til både HRT og tibolon, skal dette tydeliggøres ved at erstatte 'HRT' med 'HRT eller tibolon' i tibolon SmPC'et.

Udover tilføjelse af tekst efter tredje revision af core SPC for HRT produkter, skal nedenstående ordlyd tilføjes:

Pkt. 4.4

Under overskriften 'Ovariecancer'

I studiet 'Million Women Study' (MWS) blev det vist at den relative risiko for ovariacancer ved brug af tibolon var lig risikoen associeret ved brug af andre typer HRT

Under overskriften 'Venøs tromboemboli (VTE)'

I et epidemiologisk studie med en UK database, var risikoen for VTE i forbindelse med tibolon lavere end risikoen ved konventionelle HRT. Dog var det kun en lille andel af kvinderne der var brugere af tibolon og en lille øget risiko i forhold til ikke-brugere, kan derfor ikke udelukkes.

Under overskriften 'Lidelser i koronatarterierne (CAD)'

I et epidemiologisk studie med brug af GPRD (database) blev der ikke fundet bevis for beskyttelse mod myokardieinfarkt hos postmenopausale kvinder, der fik tibolon.

Pkt. 4.8

Under 'Brystcancer'

Tabel 2: MWS-studiet – estimeret yderligere risiko for brystcancer efter 5 års brug

| Alder (år) | Yderligere tilfælde pr. 1000 kvinder, der aldrig har brugt HRT, over en 5 års periode*2 | Risiko ratio & 95 % CI # | Yderligere tilfælde pr. 1000 HRT brugere, over en 5 års periode (95 % CI) |
|---------------------|---|--------------------------|---|
| Østrogen HRT | | | |
| 50-65 | 9-12 | 1,2 | 1-2 (0-3) |

| | | | |
|--|------|-----|---------|
| Kombineret østrogen-gestagen | | | |
| 50-65 | 9-12 | 1,7 | 6 (5-7) |
| Tibolon | | | |
| 50-65 | 9-12 | 1,3 | 3 (0-6) |
| # Overordnet risiko ratio. Risiko ratioen er ikke konstant men vil stige med længere varighed af brugen. | | | |

Under 'Ovariecancer'

Langvarig brug af østrogen HRT og kombineret østrogen-gestagen HRT er blevet forbundet med en let forøget risiko for ovariecancer. I MWS-studiet resulterede 5 års behandling med HRT i 1 ekstra tilfælde pr. 2500 brugere. Dette studie viste, at den relative risiko for ovariecancer med tibolon var den samme som risikoen med andre typer af HRT.

Under 'Lidelser i koronararterierne (CAD)'

Risikoen for lidelser i koronararterierne er let øget hos brugere af kombineret østrogen-gestagen HRT, i alderen over 60 år (se pkt. 4.4). Der er ikke bevis for, at risikoen for myokardieinfarkt med tibolon er anderledes end med andre HRT.

PL

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Udover tilføjelse af tekst efter tredje revision af core SPC for HRT produkter, skal nedenstående ordlyd tilføjes:

PIL afsnit 2:

Under overskrift 'Brystcancer'

Kvinder, der tager Livial har en lavere risiko for brystkræft end kvinder, der tager kombineret HRT og en sammenlignelig risiko med brugere af kun østrogen HRT

Under overskrift 'Ovariecancer'

Ved brug af Livial er den øgede risiko for ovariecancer ens med andre typer HRT

Under overskrift 'Blodpropper i en vene (trombose)'

Ved brug af Livial er den øgede risiko for blodprop i en vene, lavere end med andre type af HRT

Under overskrift 'Hjertesygdomme (hjerteanfald)'

Der er ikke bevis for, at HRT kan forebygge et hjerteanfald

Under overskrift 'Slagtilfælde'

Ved en 5 års observation af kvinder i halvtredserne, der ikke tager Livial, vil det forventes at gennemsnitligt 3 ud af 1000 vil få et slagtilfælde. For kvinder i halvtredserne, der tager Livial, er forventningen 7 ud af 1000 (dvs. 4 ekstra tilfælde).

Ved en 5 års observation af kvinder i tresserne, der ikke tager Livial, vil det forventes at gennemsnitligt 11 ud af 1000 vil få et slagtilfælde. For kvinder i tresserne, der tager Livial, er forventningen 24 ud af 1000 (dvs. 13 ekstra tilfælde).