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利飛亞®錠 LIVIAL®

衛署藥輸字第 021683 號
本藥須由醫師處方使用

組成
各藥錠含有 2.5 毫克的 tibolone。
有關其賦形劑請參閱 “賦形劑”。

劑型
錠劑。
為白色、斜面邊緣，圓形的扁平藥錠，直徑為 6 公釐，一面刻有“2”與“MK”，另一面有“Organon*”字樣。

臨床特性
適應症
- 自然或手術後停經引起之症狀(如潮紅、發汗、心情抑鬱、性慾降低等)。

劑量學及使用方法
使用劑量為每天一錠，無須針對老年人調整劑量。本藥錠應配水或其他飲料吞服，最好在每天的同一時間服用。
對停經症狀的初期與持續性治療，應使用最短持續期(請見“特別警告及注意事項”段)的最低有效劑量。

開始服用利飛亞錠
自然停經的婦女應至少在最後一次自然月經後的 12 個月後，才開始以利飛亞錠治療。若是手術性停經，則可立刻開始利飛亞錠的治療。

由傳統荷爾蒙替代療法轉換至使用利飛亞錠
若是由僅含雌激素藥物治療轉換時，應在完成先前的藥物療法後的第二天開始利飛亞錠治療。若由連續複合式荷爾蒙替代藥物轉換，則可在任何時候開始治療。

忘記服用藥物時
在錯過時間未超過 12 小時前，應在想起後立即服用錯過的劑量。若超過 12 小時，則省略錯過的劑量，並在正常時間服用下一錠。每錯過一次劑量就可能增加完全性出血或點狀出血的發生。

禁忌症
有下列任一情形時，不可使用利飛亞錠。若在使用利飛亞錠期間發生下列任一狀況，則應立即停止治療。
- 懷孕與哺乳。
- 確知、曾經或疑似患有乳癌-在一個有安慰劑對照組研究試驗中顯示利飛亞錠會增加乳癌復發的危險性。
- 確知或疑似罹患雌激素依賴性惡性腫瘤時(如子宮內膜癌)。
- 不明原因的陰道出血。
- 未作治療的子宮內膜增生。
- 先前或目前患有靜脈血栓栓塞(指深層靜脈血栓塞、肺栓塞)。
- 已知的易發血栓疾病(如蛋白質 C、蛋白質 S 或抗凝血酶缺乏症，請見“特別警告及注意事項”段)。
- 任何患有動脈血栓性栓塞疾病(如心絞痛、心肌梗塞、中風或暫時性缺血性發作(TIA))病史者。
- 急性肝臟疾病，或有肝病病史經肝功能測試尚未回復正常者。
- 已知對主成分或任何賦形劑過敏者。
- 紫質沉著症。

特別警告及注意事項
以利飛亞錠治療時，不可各別加入黃體素。
應該在停經症候群症狀對生活品質產生負面影響時，才考慮使用利飛亞錠，而且至少每年詳細評估該療法的優缺點，只有在優點多於缺點時才建議繼續採用利飛亞錠。
具完整子宮的婦女方面，應從她們對治療、發病率與致死率的反應的觀點，根據個別危險因子與牢記癌症與中風的頻率與特性，對其中風、乳癌與子宮內膜癌的危險性作審慎評估(請見“不良反應”段)。
使用荷爾蒙替代療法(Hormone Replacement Therapy; HRT)或 tibolone 治療早發性停經之相關風險方面的證據相當有限。不過，由於較年輕之婦女的絕對風險極低，因此，和較年長的婦女相比較，風險效益權衡的結果可能對這些較年輕的婦女較為有利。
<u>健康檢查/追蹤</u>
- 在初用或重新使用荷爾蒙替代療法或 tibolone 時，應建立完整的個人與家族醫療史。藉由病史、使用禁忌症與警語來制定適當的身體(含子宮頸與乳房)檢查。在治療期間，應針對婦女個別情況來建議其定期檢查的頻率與種類。應教導婦女所有乳房的變化務必告知醫師或護士(請見如下“乳癌”)。應根據目前可被接受篩檢的規範，依個別臨床需求而調整後，來執行臨床檢查，包括合適的造影工具，如乳房攝影。

<u>須作監測的情況</u>
- 若病患出現、曾發生、或/和在懷孕或之前荷爾蒙治療期間引起以下任何一種情況時，應給予嚴密的監測，須考慮到這些狀況可能會在利飛亞錠治療期間再發生或者加重，特別是
  - 平滑肌瘤(子宮纖維肌瘤)或子宮內膜異位
  - 血栓疾病(如下)的危險因子
  - 雌激素依賴性腫瘤危險因子，如第一級遺傳性乳癌危險族群
  - 高血壓
  - 肝臟疾病(如：肝腺瘤)
  - 有或無血管狀況的糖尿病
  - 膽結石
  - 偏頭痛或(嚴重)頭痛
  - 全身性紅斑性狼瘡
  - 子宮內膜的過度增生病史
  - 癲癇症
  - 氣喘
  - 耳硬化症

<u>立刻停止治療的原因：</u>
<u>如果發現禁忌症與以下情形，須立刻停止治療：</u>
- 黃膽症或肝功能變差
- 血壓明顯上升
- 偏頭痛發生

<u>子宮內膜增生及子宮內膜癌：</u>
- 自隨機控制試驗的有效數據中，呈現結果並不一致。無論如何，觀察性的研究已一致性的顯示出，在正常臨床診療中，女性使用利飛亞錠會增加罹患子宮內膜癌的風險(請見“不良反應”段)。而在這些研究中，隨著使用期間增加風險也跟著上升。當以陰道穿透超音波檢查時，Tibolone 會增加子宮內膜壁的厚度。
- 在第一個月治療時可能會有間歇性出血與點狀出血的發生(請見“藥物效力學特性”段)，任何若在治療 6 個月後仍持續出血，或超過 6 個月後才開始，或在停止治療後還持續出血的情況，應要求婦女報告醫師。此使用婦女應執行婦科檢查，如子宮內膜生化檢查來排除子宮內膜惡性腫瘤的危險。

<u>乳癌</u>
- 有關罹患乳癌危險性與 Tibolone 相關聯的證據尚不明確。百萬婦女研究(Million Women Study/ MWS)已證實罹患乳癌危險性的顯著增加是與使用 2.5mg 劑量相關。此危險性在用藥數年內就會顯現，而且隨著服用期間加長而提高，但是在停止治療後的幾年(最多 5 年)

就會回到基準點(參見"不良反應"段)。但此結果在普遍性資料研究(General Practice Research Database study; GPRD)中，並無法被確認。

卵巢癌

- 卵巢癌要比乳癌罕見得多。長期(至少 5~10 年)使用單一雌激素荷爾蒙替代療法會些微增加罹患卵巢癌的危險(參見"不良反應"段)。有些研究(包括婦女健康關懷[Women Health Initiative trial; WHI]試驗)顯示，長期使用複合式 HRTs 所帶來的風險可能較使用安慰劑相當或略低(參見"不良反應"段)。百萬婦女研究的結果顯示，使用 tibolone 時發生卵巢癌的相對風險和使用其它類型之 HRT 時的風險大致相當。

靜脈血栓栓塞症

- 雌激素或雌激素-黃體素複合式荷爾蒙替代療法(HRT)有 1.3-3 倍的危險會發生靜脈血栓栓塞(Venus Thromboembolism; VTE)，例如深層靜脈栓塞或肺栓塞。和治療 1 年之後相比較，此類事件較可能會發生於使用 HRT 治療的第 1 年期間(參見"不良反應"段)。利用一個英國資料庫所進行的流行病學研究顯示，使用 tibolone 時伴隨發生 VTE 的風險要比使用傳統 HRT 時的風險低，但當時只有一小部份的婦女使用 tibolone，因此並不能排除其風險會較非使用者小幅升高的可能性。
- 已知有血栓栓塞情況的患者，罹患 VTE 的危險性較高，且 HRT 或 tibolone 可能增加其危險性。因此 HRT 禁用於此類病患(請見"禁忌症"段)。
- 一般公認的VTE危險因子包括雌激素的使用、較大的年紀、重大手術、長時間固定不動、嚴重肥胖(體重質量指數>30kg/m^2)、懷孕/產後期間、全身性紅斑性狼瘡(SLE)與癌症。目前有關靜脈曲張在VTE中的角色並無共識。和所有的手術後患者一樣，應考慮事先採取預防措施，以免手術後發生VTE。如果在接受非緊急手術後會有一段較長的時間無法活動，建議在手術前 4 至 6 週即暫時停用HRT或tibolone。應待婦女能夠自由活動之後再重新開始治療。
- 對本身無 VTE 病史但有一位一等親在年輕時有血栓病史的婦女，可於詳細說明篩檢的限制(篩檢只能發現一部份的易血栓缺陷)之後進行篩檢。如果發現有一種易血栓缺陷是其家庭成員發生血栓症的主因，或者是一種「嚴重的」缺陷(如抗凝血酶、蛋白質 S 或蛋白質 C 缺乏症，或併有數種缺陷)，則禁止使用 HRT 或 tibolone。
- 對已在使用抗凝血劑治療的婦女，應審慎權衡使用 HRT 或 tibolone 的效益與風險。
- 如果在初始治療後即發生 VTE，應予停藥。應教導患者若有疑似血栓栓塞症狀(如腿部疼痛腫大、胸部突然疼痛、呼吸困難)時，立即通知醫師。

冠狀動脈疾病(CAD)

- 並無隨機控制臨床研究的證據證實使用複合式雌激素-黃體素 HRT 或僅含雌激素的 HRT 治療對原先即患有或未患有 CAD 之婦女的心肌梗塞預防效果。在一項利用 GPRD 所進行的流行病學研究中，並未發現任何證據顯示接受 tibolone 治療的停經後婦女可達到預防心肌梗塞的效果。

缺血性中風

- Tibolone 自治療的第一年會增加缺血性中風的危險(請參閱"不良反應"段)。中風危險的基準線為高度年齡依賴型，所以 tibolone 的影響對年長者較大。

其他

- 具半乳糖不耐症、Lapp 乳糖酶缺乏、乳糖-半乳糖吸收不良等罕見遺傳疾病的病患不可使用本藥。
- 利飛亞錠不得作避孕用。
- 以利飛亞錠治療會引起顯著劑量相關性的降低高密度脂蛋白膽固醇 HDL-cholesterol(兩年後，自 1.25mg 劑量的-16.7%至 2.5mg 劑量的-21.8%)、總三酸甘油脂與脂蛋白血中濃度也會降低。對總三酸甘油脂與極低密度脂蛋白膽固醇(VLDL-C)的降低則與劑量無關，對低密度脂蛋白膽固醇(LDL-C)則不影響。這些發現的臨床含義尚未知。
- 雌激素可能會引起體液滯留，因此需謹慎觀察心臟或腎臟功能不佳的患者。
- 有極少案例以雌激素治療時由於血中三酸甘油脂大量增加導致胰臟炎的報告之情況，因此有高三酸甘油脂的婦女在採用雌激素或荷爾蒙替代療法期間應作嚴密追蹤。
- 利飛亞錠會些微減少甲狀腺結合球蛋白(Thyroid binding globulin; TBG)與總 T4 值，總 T3 值則不變。利飛亞錠降低性荷爾蒙結合球蛋白(sex-hormone-binding globulin; SHBG)，然而不影響腎上腺皮質結合球蛋白與循環中的氫化腎上腺皮脂醇濃度。
- 使用 HRT 並不能改善認知功能。有一些證據顯示，在 65 歲之後開始使用連續複合式 HRT 或僅含雌激素之 HRT 治療的婦女中，出現失智症可能病例的風險有升高的現象。

與其他藥物間的交互作用及其他形式的交互作用

因為利飛亞錠可能增加血中的纖維蛋白的溶解作用，因而可能增強抗凝血劑的作用，與 warfarin 併用時已得知有此作用。因此在合併使用利飛亞錠及抗凝血劑時，應予以警示。必要時應調整 warfarin 的劑量。

在 tibolone 的藥物動力學交互作用方面，現有的資料相當有限。一體內研究顯示 tibolone 的同時治療對細胞色素 P450 3A4 受質 Midazolam 的藥動學具中度影響。因此可預期到與其他的 CYP3A 受質的交互作用。

具CYP3A4誘導作用的藥物，如barbiturates、carbamazepine、hydantoins與rifampicin，可能會增強tibolone的代謝作用，從而影響其治療效果。

草藥製劑，包括聖約翰草(Hypericum Perforatum)，可能會誘導雌激素與黃體素透過 CYP3A4 代謝的作用。臨床上，雌激素與黃體素的代謝作用增強可能會導致療效降低，並使子宮出血概況發生改變。

懷孕及哺乳

懷孕期間禁止使用利飛亞錠(請參閱"禁忌症")。倘若在利飛亞錠服用期間懷孕，應立刻終止治療。尚無利飛亞錠用於懷孕婦女的臨床資料，但動物研究顯示利飛亞錠具有生殖毒性(請參閱"前臨床安全資料")。對於人的可能危險則未知。

哺乳期間禁忌使用利飛亞錠(請參閱"禁忌症")。

對開車及使用機械能力的影響

利飛亞錠對於警覺性及精神集中力之影響尚未知。

不良反應

此章節中說明在 21 個有安慰劑對照組研究試驗中(包括 LIFT study)所發現的不良影響，這些研究總共包括 4079 個接受利飛亞錠有效劑量(1.25 或 2.5 毫克)的婦女以及 3476 個接受安慰劑的婦女，治療期由 2 個月到 4.5 年不等。表<一>列有以利飛亞錠治療的婦女，在統計上明顯高於接受安慰劑者的不良反應。

表 <一>　利飛亞錠的不良反應

系統器官種類	常見	不常見
	>1%, <10%	>0.1%, <1%
胃腸道	下腹痛	
皮膚與皮下組織症狀	毛髮生長異常	面皰
生殖系統與乳房症狀	陰道分泌	乳房不適

	子宮內膜壁增厚	黴菌感染
	停經後異常出血	陰道黴菌感染
	乳房觸痛	乳頭疼痛
	陰部搔癢	
	陰道念珠球菌感染	
	陰道出血	
	骨盆腔疼痛	
	子宮頸異常	
	生殖器分泌	
	外陰道炎	
研究	體重增加	
	子宮頸抹片異常*	

*其主要是因為良性的改變所造成，服用利飛亞錠群組相較於安慰劑組其子宮頸病理反應(子宮頸癌)並未增加。

在市場使用上，其他已被發現的不良反應包括如：頭暈、發疹、搔癢、脂漏性皮膚病、頭痛、偏頭痛、視覺障礙(包括視力模糊)、胃腸道不適、憂鬱、水腫、肌肉骨骼系統的不適：如關節痛或肌痛，以及肝功能指數改變。

乳癌風險

- 報告指出，在使用複合式雌激素-黃體素療法治療超過5年的婦女中，經診斷確定發生乳癌的風險會升高達2倍。
- 在僅使用雌激素及使用tibolone的患者中，風險升高的幅度都明顯低於合併使用雌激素-黃體素的患者。
- 風險的高低程度取決於使用時間的長短(請參閱"特別警告及注意事項"段)。
- 最大型之流行病學研究(MWS)的結果如下所示。

表 <二> 百萬婦女研究(MWS) – 使用5年後，發生乳癌的估計額外風險

年齡範圍(歲)	在5年期間，每1000名非HRT使用者中增加的病例數	風險比率與95%CI[#]	在5年期間，每1000名HRT使用者相較於非HRT使用者中增加的病例數(95%CI)
僅含雌激素的HRT			
50至64歲	9-12	1.2	1-2 (0-3)
合併使用雌激素-黃體素			
50至64歲	9-12	1.7	6 (5-7)
Tibolone			
50至64歲	9-12	1.3	3 (0-6)

[#]整體風險比率。此風險比率並不具一致性，但會隨使用時間延長而升高。

子宮內膜癌風險

在保有子宮但未使用HRT或tibolone的婦女中，發生子宮內膜癌的風險約為每1000人5例。

在隨機、安慰劑控制的試驗其中含在納入時未作子宮內膜異常篩檢的婦女，因此反應在臨床診斷上，發現子宮內膜癌的高度風險(LIFT試驗，平均年齡68歲)。在在此臨床試驗的2.9年後，相對於利飛亞錠組(n=1,746)有4例子宮內膜癌的案例，安慰劑組(n=1,733)則沒有子宮內膜癌的案例被診斷出來。相當於此試驗中每年每1000名使用利飛亞錠的婦女有0.8名額外的案例被診斷出子宮內膜癌(請參閱"特別警告和注意事項"段)。

缺血性中風風險

- 發生缺血性中風的相對風險並不取決於年齡或使用時間的長短，但由於基礎風險有強烈的年齡依賴性，因此，使用HRT或tibolone之婦女發生缺血性中風的整體風險會隨年齡而升高，參見"特別警告及注意事項"段。
- 一個為期2.9年隨機控制研究，已評量出使用1.25mg利飛亞錠的婦女(28/2249)相較於使用安慰劑的婦女(13/2257)發生中風的危險會增加2.2倍(平均年齡68歲)。多數為缺血性中風。
- 中風的風險基準為高度年齡-依賴性。因此，基本上在5年內發生中風的病例數：年紀為50~59歲者每1000位約3人；年紀為60~69歲者每1000位約有11人。對使用tibolone 5年的婦女而言，所增加的中風病例數，估計年紀為50~59歲者每1000位約4人，年紀為60~69歲者每1000位約13人。

其餘曾報告與雌激素及雌激素-黃體素治療有關的不良反應有：

- 長期使用僅含雌激素的HRT及複合式雌激素-黃體素HRT治療會使發生卵巢癌的風險略為升高。在百萬婦女研究中，使用HRT治療5年會使每2500名使用者中的病例數額外增加1例。這項研究顯示，使用tibolone時發生卵巢癌的相對風險和使用其它類型之HRT時的風險大致相當。
- HRT與提高發生靜脈血栓栓塞(VTE)1.3-3倍的風險有關，例如深層靜脈栓塞或肺栓塞。此類事件較可能會發生於使用HRT治療的第1年期間(請見"特別警告及注意事項")。WHI研究的結果如下所示：

表 <三> WHI研究 – 在5年使用期間發生VTE的額外風險

年齡範圍(歲)	在5年期間，安慰劑組中每1000名婦女的發生率	風險比率與95%CI	每1000名HRT使用者中增加的病例數
僅使用口服用的雌激素*			
50至59歲	7	1.2 (0.6-2.4)	1 (-3-10)
合併使用口服用的雌激素-黃體素			
50至59歲	4	2.3 (1.2–4.3)	5 (1-13)

*針對無子宮之婦女所進行的研究

- 60歲以上並使用複合式雌激素-黃體素HRT治療的患者中，發生冠狀動脈疾病的風險有略為升高的現象(請見"特別警告及注意事項")。並無任何證據顯示使用tibolone時發生心肌梗塞的風險不同於使用其他HRT時的風險。
- 膽囊疾病。
- 皮膚與皮下疾病：黃褐斑、多形性紅斑、結節性紅斑、血管紫斑。
- 有些證據顯示在65歲以後開始持續使用複合式HRT或雌激素HRT，會增加癡呆症發生的風險(參考"特殊警告與注意事項"章節)。

藥物過量

Tibolone對動物的急性毒性非常低，即使是同時服用多顆的藥錠或膠囊，也不致於發生中毒症狀。急性過量時，可能會出現噁心、嘔吐及女性陰道出血症狀。目前尚無專一解毒劑，在必要時可針對症狀給予治療。

藥理學特性

藥物效力學特性

ATC code: G03CX01

在口服後，tibolone很快被代謝成3種化學物，這3種化學物均對利飛亞錠的藥效學有所貢獻。其中2種代謝物(3α-OH-tibolone及3β-OH-tibolone)具有雌激素活性，而第3種代謝物(Δ^4-isomer of tibolone)具有黃體素及雄激素活性。

利飛亞錠可作為無法再製造雌激素的更年期婦女的代用品與緩解停經症候群。利飛亞錠可預防更年期或卵巢切除後的骨質流失。

利飛亞錠臨床試驗資料

- 緩解雌激素不足症候群。
  - 在使用後的前幾週期間就可緩解停經症候群。
- 在子宮內膜的作用與出血方式
  - 使用利飛亞錠治療的病患，有子宮內膜癌與子宮內膜增生的案例發生(請參閱"特別警告和注意事項"及"不良反應"段)。
  - 88%使用 2.5mg 利飛亞錠的婦女在治療 12 個月後，會呈現出無月經的現象。治療期的前 3 個月，32.6%有出現出血和/或點狀出血症狀。在使用 11-12 個月，有 11.6%出現出血和/或點狀出血症狀。
- 作用於乳房
  - 臨床研究，相較於安慰劑組，以 Livial 治療的婦女其乳房攝影密度不會增加。

藥動學特性

在口服後，tibolone迅速且大量的被吸收。由於其快速地被代謝，因此血漿中tibolone的濃度極低。血漿中Tibolone的Δ^4-isomer的濃度也非常低，因此一些藥動學參數無法被偵測。3α-OH及 3β-OH代謝物的最高血漿濃度較高，但無累積性。

表<四> 利飛亞錠的藥動學參數

	tibolone		3α-OH metabolite		3β-OH metabolite		Δ^4-isomer	
	SD	MD	SD	MD	SD	MD	SD	MD
C_{max} (ng/ml)	1.37	1.72	14.23	14.15	3.43	3.75	0.47	0.43
$C_{average}$	-	-	-	1.88	-	-	-	-
T_{max} (h)	1.08	1.19	1.21	1.15	1.37	1.35	1.64	1.65
$T_{1/2}$ (h)	-	-	5.78	7.71	5.87	-	-	-
C_{min} (ng/ml)	-	-	-	0.23	-	-	-	-
AUC_{0-24} (ng/ml.h)	-	-	53.23	44.73	16.23	9.20	-	-

SD=single dose; MD=multiple dose

Tibolone 主要是以結合代謝物(大部分是 sulfated)的形式排泄，服入的藥物一部份排泄於尿液中，但大部分經由糞便排出。

食物之攝取對於此藥物吸收程度沒有顯著影響。

已知 Tibolone 與其代謝物的藥物動力參數並不受腎功能影響。

前臨床安全性資料

在動物研究中，tibolone 因其荷爾蒙特性而有抗懷孕與胚胎毒性。Tibolone 對於小白鼠及大白鼠均不會有致畸性，但是當使用量達流產劑量時則對兔子有致畸形的可能(請見"懷孕與哺乳")。體內試驗 Tibolone 無基因毒性。即使有一致癌性反應出現在某些種類的大白鼠(肝腫瘤)與小白鼠(膀胱瘤)，但其臨床的相關性仍未確立。

藥物特性

賦形劑

利飛亞錠的 2.5 毫克藥錠含有馬鈴薯澱粉、硬脂酸鎂、抗壞血酸棕櫚酸(酯性維他命 C)及乳糖。

不相容性

無。

儲存期限

請見外盒標示。

儲存之特別注意事項

以原包裝及外盒儲存於 2-25 °C 之間。

容器的材質及內容物

利飛亞錠的 2.5 毫克藥錠包裝於按壓推出盒中，此按壓式包裝為透明的 polyvinyl chloride 膜片及有色 aluminum foil 包含與藥錠接觸面有一熱密封層。目前有下列的包裝可供使用：每盒中有 1 或 3 片，每片有 28 顆白色藥錠，每一藥錠含有 2.5 毫克的 tibolone。

本版本修定日期

2012 年 1 月

製造廠：N.V.Organon.

廠　址：Kloosterstraat 6, 5349 AB Oss, the Netherlands.

藥　商：美商默沙東藥廠股份有限公司台灣分公司

地　址：台北市信義路五段 106 號 12 樓

1. NAME OF THE MEDICINAL PRODUCT

Livial 2.5 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of tibolone.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, round and flat tablets with beveled edges and a diameter of 6 mm and coded “MK” above “2” on one side and “Organon∗” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after menopause.

4.2 Posology and method of administration

The dosage is one tablet per day. No dose adjustment is necessary for the elderly. The tablets should be swallowed with some water or other drink, preferably at the same time every day.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

Starting Livial

Women experiencing a natural menopause should commence treatment with Livial at least 12 months after their last natural bleed. In case of a surgical menopause, treatment with Livial may commence immediately.

Switching from a sequential or continuous combined HRT preparation

If changing from a sequential HRT preparation, treatment with Livial should start the day following completion of the prior regimen. If changing from a continuous-combined HRT preparation, treatment can start at any time.

Missed dose

A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case, the missed dose should be skipped and the next dose should be taken at the normal time. Missing a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Pregnancy and lactation
- Known, past or suspected breast cancer - Livial increased the risk of breast cancer recurrence in a placebo-controlled trial
- Known or suspected estrogen-dependent malignant tumors (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- Any history of arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke or TIA)
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to the active substance or to any of the excipients
- Porphyria

4.4 Special warnings and precautions for use

A separate progestogen should not be added with Livial treatment.
For the treatment of postmenopausal symptoms, Livial should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and Livial should only be continued as long as the benefit outweighs the risk.
The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer (see below and section 4.8) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers and stroke, in terms of their response to treatment, morbidity and mortality.
Evidence regarding the risks associated with HRT or tibolone in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.
<u>Medical examination/follow-up</u>

- Before initiating or reinstituting HRT or tibolone, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this

and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Livial, in particular:
  - Leiomyoma (uterine fibroids) or endometriosis
  - Risk factors for thromboembolic disorders (see below)
  - Risk factors for estrogen dependent tumors, e.g. 1st degree heredity for breast cancer
  - Hypertension
  - Liver disorders (e.g. liver adenoma)
  - Diabetes mellitus with or without vascular involvement
  - Cholelithiasis
  - Migraine or (severe) headache
  - Systemic lupus erythematosis
  - A history of endometrial hyperplasia (see below)
  - Epilepsy
  - Asthma
  - Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache

Endometrial hyperplasia and carcinoma

- The available data from randomized controlled trials are conflicting, however, observational studies have consistently shown that women who are prescribed Livial in normal clinical practice are at an increased risk of having endometrial cancer diagnosed (see also Section 4.8). In these studies risk increased with increasing duration of use. Tibolone increases endometrial wall thickness, as measured by transvaginal ultrasound.
- Break-through bleeding and spotting may occur during the first months of treatment (see section 5.1). Women should be advised to report any break-through bleeding or spotting if it is still present after 6 months of treatment, if it starts beyond that time or if it continues after treatment has been discontinued. The woman should be referred for gynecological investigation, which is likely to include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

- Evidence with respect to breast cancer risk in association with tibolone is inconclusive. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2.5mg dose. This risk became apparent within a few years of use and increased with duration of intake, returning to baseline within a few (at most five) years after stopping treatment, see section 4.8. These results could not be confirmed in a study using the General Practice Research Database (GPRD).

Ovarian cancer

- Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of estrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the Women's Health Initiative (WHI) trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller risk than placebo (see section 4.8). 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.

Venous thromboembolism

- Estrogen or estrogen-progestogen HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8). 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.

- Patients with known thrombophilic states have an increased risk of VTE and HRT or tibolone may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- Generally recognized risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT or tibolone 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT or tibolone is contraindicated.
- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or tibolone.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Ischaemic stroke

- Tibolone increases the risk of ischaemic stroke from the first year of treatment (see section 4.8). The baseline risk of stroke is strongly age-dependent and so the effect of tibolone is greater with older age.

Other conditions

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Livial is not intended for contraceptive use.
- Treatment with Livial results in a marked dose-dependent decrease in HDL cholesterol (from -16.7% with a 1.25 mg dose to -21.8% for the 2.5 mg dose after 2 years). Total triglycerides and lipoprotein(a) levels were also reduced. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged. The clinical implication of these findings is not yet known.
- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Treatment with Livial results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. Livial decreases the level of sex-hormone-binding globulin (SHBG), whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

4.5 Interaction with other medicinal products and other forms of interaction

Since Livial may increase blood fibrinolytic activity, it may enhance the effect of anticoagulants. This effect has been demonstrated with warfarin. Caution should therefore be exercised during the simultaneous use of Livial and anticoagulants, especially when starting or stopping concurrent Livial treatment. If necessary, the dose of warfarin should be adjusted.

There is limited information regarding pharmacokinetic interactions with tibolone. An *in vivo* study showed that simultaneous treatment of tibolone affects pharmacokinetics of the cytochrome P450 3A4 substrate midazolam to a moderate extent. Based on this, drug interactions with other CYP3A4 substrates might be expected.

CYP3A4 inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus affect its therapeutic effect.

Herbal preparations containing St.John`s wort (Hypericum Perforatum) may induce the metabolism of oestrogens and progestagens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Pregnancy and lactation

Livial is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during medication with Livial, treatment should be withdrawn immediately. For Livial no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Livial is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Livial is not known to have any effects on alertness and concentration.

4.8 Undesirable effects

This section describes undesirable effects, which were registered in 21 placebo-controlled studies (including the LIFT study), with 4079 women receiving therapeutic doses (1.25 or 2.5 mg) of Livial and 3476 women receiving placebo. The duration of treatment in these studies ranged from 2 months to 4.5 years. Table 1 shows the undesirable effects that occurred statistically significantly more frequently during treatment with Livial than with placebo.

Table 1 Undesirable effects of Livial

System organ class	Common >1%,<10%	Uncommon >0.1%,<1%
Gastrointestinal disorders	Lower abdominal pain	
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne
Reproductive system and breast disorders	Vaginal discharge	Breast discomfort
	Endometrial wall thickening	Fungal infection
	Postmenopausal haemorrhage	Vaginal mycosis
	Breast tenderness	Nipple pain
	Genital pruritus	
	Vaginal candidiasis	
	Vaginal haemorrhage	
	Pelvic pain	
	Cervical dysplasia	
	Genital discharge	
	Vulvovaginitis	
Investigations	Weight increase	
	Abnormal cervical smear*	

* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with Livial compared to placebo.

In market use, other undesirable effects that have been observed include:
dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, edema, effects on the musculoskeletal system such as arthralgia or myalgia and changes in liver function parameters.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of estrogen-only and tibolone therapy is substantially lower than that seen in users of estrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest epidemiological study (MWS) are presented.

Table 2 Million Women study – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period	Risk ratio & 95%CI#	Additional cases per 1000 HRT users compared to never-users of HRT over 5 years (95%CI)
Estrogen only HRT			
50-64	9-12	1.2	1-2 (0-3)
Combined estrogen-progestagen			
50-64	9-12	1.7	6 (5-7)
Tibolone			
50-64	9-12	1.3	3 (0-6)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use.			

Endometrial cancer risk

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT or tibolone.

The randomized placebo controlled trial that included women who had not been screened for endometrial abnormalities at baseline, and therefore reflected clinical practice, identified the highest

risk of endometrial cancer, (LIFT study, mean age 68 years). In this study, no cases of endometrial cancer were diagnosed in the placebo group (n=1,773) after 2.9 years compared with 4 cases of endometrial cancer in the Livial group (n=1,746). This corresponds to a diagnosis of 0.8 additional case of endometrial cancer in every 1000 women who used Livial for one year in this study (see section 4.4).

Risk of ischaemic stroke

- The relative risk of ischaemic stroke is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of ischaemic stroke in women who use HRT or tibolone will increase with age, see section 4.4.
- A 2.9 year randomized controlled study has estimated a 2.2-fold increase in the risk of stroke in women (mean age 68 years) who used 1.25 mg Livial (28/2249) compared with placebo (13/2257). The majority (80%) of strokes were ischaemic.
- The baseline risk of stroke is strongly age-dependent. Thus, the baseline incidence over a 5 year period is estimated to be 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years.
- For women who use Livial for 5 years, the number of additional cases would be expected to be about 4 per 1000 users aged 50-59 years and 13 per 1000 users aged 60-69 years.

Other adverse reactions have been reported in association with estrogen and estrogen-progestogen treatment:

- 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.
- HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

Table 3 WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-progestagen			
50-59	4	2.3 (1.2–4.3)	5 (1-13)

*Study in women with no uterus

- The risk of coronary artery disease is slightly increased in users of combined estrogen-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.
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Some evidences demonstrate that starting estrogen-only or combined estrogen-progestagen HRT continuously over the age of 65 has been associated with an increased risk of dementia (see section 4.4).

4.9 Overdose

The acute toxicity of tibolone in animals is very low. Therefore, toxic symptoms are not expected to occur, even when several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting and vaginal bleeding in females may occur. No specific antidote is known. Symptomatic treatment can be given if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CX01

Following oral administration, tibolone is rapidly metabolized into three compounds, which all contribute to the pharmacodynamic profile of Livial. Two of the metabolites (3α-OH-tibolone and 3β-OH-tibolone) have estrogenic-like activities, whereas the third metabolite (Δ4-isomer of tibolone) has progestogenic and androgenic-like activities.

Livial substitutes for the loss of estrogen production in postmenopausal women and alleviates menopausal symptoms. Livial prevents bone loss following menopause or ovariectomy.

Clinical trial information of Livial:

- Relief of estrogen-deficiency symptoms

- Relief of menopausal symptoms generally occurs during the first few weeks of treatment.

- Effects on the endometrium and bleeding patterns
  - There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with Livial (see section 4.4 and 4.8).
  - Amenorrhea has been reported in 88% of women using Livial 2.5 mg after 12 months of treatment. Breakthrough bleeding and/or spotting has been reported in 32.6% of women during the first 3 months of treatment, and in 11.6% of women after 11-12 months of use.
- Effects on the breast
  - In clinical studies mammographic density is not increased in women treated with Livial compared to placebo.

5.2 Pharmacokinetic properties

Following oral administration, tibolone is rapidly and extensively absorbed. Due to rapid metabolism, the plasma levels of tibolone are very low. The plasma levels of the Δ4-isomer of tibolone are also very low. Therefore some of the pharmacokinetic parameters could not be determined. Peak plasma levels of the 3α-OH and the 3β-OH metabolites are higher but accumulation does not occur.

Table 4 Pharmacokinetic parameters of Livial (2.5 mg)

	tibolone		**3α-OH metabolite**		**3β-OH metabolite**		**Δ4-isomer**	
	SD	MD	SD	MD	SD	MD	SD	MD
C_{max} (ng/ml)	1.37	1.72	14.23	14.15	3.43	3.75	0.47	0.43
$C_{average}$	--	--	--	1.88	--	--	--	--
T_{max} (h)	1.08	1.19	1.21	1.15	1.37	1.35	1.64	1.65
$T_{1/2}$ (h)	--	--	5.78	7.71	5.87	--	--	--
C_{min} (ng/ml)	--	--	--	0.23	--	--	--	--
AUC_{0-24} (ng/ml.h)	--	--	53.23	44.73	16.23	9.20	--	--

SD = single dose; MD = multiple dose

Excretion of tibolone is mainly in the form of conjugated (mostly sulfated) metabolites. Part of the administered compound is excreted in the urine, but most is eliminated via the feces.
The consumption of food has no significant effects on the extent of absorption.
The pharmacokinetic parameters for tibolone and its metabolites were found to be independent of renal function.

5.3 Preclinical safety data

In animal studies, tibolone had anti-fertility and embryotoxic activities by virtue of its hormonal properties. Tibolone was not teratogenic in mice and rats. It displayed teratogenic potential in the rabbit at near-abortive dosages (see section 4.6). Tibolone is not genotoxic under *in vivo* conditions. Although a carcinogenic effect was seen in certain strains of rat (hepatic tumors) and mouse (bladder tumors), the clinical relevance of this is uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Livial 2.5 mg tablets contain potato starch, magnesium stearate, ascorbyl palmitate and lactose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please see outer carton.

6.4 Special precautions for storage

Store in the original package and in the outer carton at 2-25 °C.

6.5 Nature and contents of container

Livial 2.5 mg tablets are packed in push-through packs of transparent polyvinyl chloride film and colored aluminum foil containing a heat seal coating on the side in contact with the tablets. The following pack sizes are available: cardboard boxes containing 1 or 3 push-through packs with 28 white tablets each containing 2.5 mg of tibolone.

6.6 Instructions for use and handling <and disposal>

Not applicable.

7. DATE OF REVISION OF THE TEXT

January 2012