

諮詢您的醫生LENVIMA[®] 能否是您的治療選擇

LENVIMA是在肝細胞癌 (HCC) 無法藉手術割除時，單獨使用的首項處方治療藥物。



部分重要安全資訊

LENVIMA可能引發嚴重的副作用，包括：

- **高血壓 (血壓高)：**高血壓是使用LENVIMA的常見副作用，並且可能很嚴重。在開始服用LENVIMA前，您的血壓應受到良好的控制。醫療保健提供者應在您使用LENVIMA治療期間，定期檢查您的血壓；若血壓出現問題，您的醫療保健提供者可能會處方藥物，治療高血壓

 **LENVIMA[®]**
(lenvatinib) capsules | 10 mg and 4 mg

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。

了解肝癌



肝癌風險因素



肝細胞癌，或簡稱 HCC，是肝癌的最常見類型，約佔原發性肝癌的 80%。始於肝臟的癌症謂之原發性肝癌。被診斷患上肝癌後感到不知所措是完全正常的。但可能有助肝癌晚期患者的藥物是存在的。

您的治療計劃取決於癌症的階段，其他健康因素以及肝癌的根本誘因。

肝癌有兩大階段 — 早期和晚期。

- 早期的肝癌可通過手術或移植治療，並有可能治愈
- 晚期肝癌通常不能通過手術治療

以下是為何癌症可能未必能通過手術治療的一些原因：

- 癌細胞已擴散到整個肝臟
- 腫瘤在肝臟的位置使之難於切除
- 病人健康欠佳，無法接受手術
- 病人拒絕接受手術

即使晚期肝癌也有治療的可能。與您的醫生討論治療方案的選擇。



某些人由於擁有潛在因素，他們會比一般人更容易患上某種病 — 此謂風險因素。

肝癌的潛在風險因素有數個。某些風險因素，如吸煙，是生活方式上的選擇；其他，如您的族裔，是您控制不了的。右邊的列表包括一些最常見的風險因素，但並不全面。請與您的醫生談談哪些風險因素與您是可能最相關的。

乙型肝炎病毒 (HBV)

慢性乙肝可以導致肝臟的炎症和損害，稱為肝硬化。大多數肝硬化患者會發生肝癌



糖尿病

在美國亞裔人士中的未確診糖尿病比例最高 (50%)。糖尿病會增加患肝癌的風險

吸煙

吸煙與患肝癌的可能性增加有關

酒精

大量飲酒者患肝癌的可能性增加五倍

暴露於黃曲霉毒素

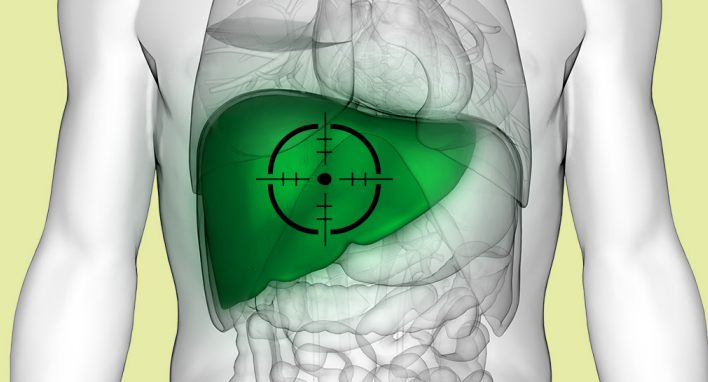
一些移民到美國的亞洲人，來自於受有毒物質黃曲霉毒素影响的國家。黃曲霉毒素是在植物產品上生長的黴菌，如花生、穀物或玉米

欲了解有關這些風險因素的更多信息，請訪問 www.OurLenvima.com/risk-chinese

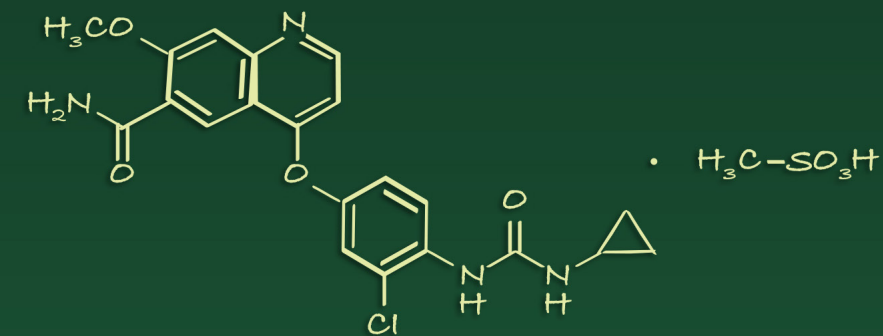


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什麼是 LENVIMA?



LENVIMA 如何發揮作用?



如果LENVIMA被處方用於治療無法通過手術切除的肝細胞癌，那麼您可能會發現以下信息會有所幫助。

LENVIMA是經FDA批准的，在無法通過手術割除肝細胞癌時，可被單獨使用的一線處方藥物



一天一次，每天在家中服用的口服膠囊

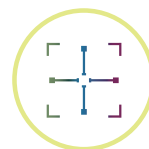


LENVIMA膠囊，一天一次，每天同一時間服食，隨餐或空腹都可以。若吞服膠囊有困難，則可將膠囊溶於水或果汁中服食。

尚不清楚LENVIMA對兒童是否安全有效。

靶向治療

LENVIMA不是化療，而是一種稱為靶向療法的藥物。一如其名，它以癌細胞內某些導致細胞生長和繁殖的蛋白質為目標。但由於健康細胞也含有這些蛋白質，LENVIMA會影響某些健康細胞，因此可能會導致嚴重的副作用。



據信，LENVIMA是通過干擾腫瘤在體內生長和生存所需的過程而發揮作用的。

它在體內兩處發揮此作用：

在細胞中

據信，LENVIMA干擾細胞試圖生存和繁殖的方式。



在血管內

LENVIMA還被認為會損害血管增長所需的某些活動。腫瘤的生存和增長需要血管支持。



LENVIMA也會影響健康的細胞，因而導致嚴重的副作用。

欲了解更多有關LENVIMA如何發揮作用的信息，請訪問
www.OurLenvima.com/work-chinese



部分重要安全資訊

LENVIMA可能會引起嚴重的副作用，包括（續）：

- **心臟問題：**LENVIMA可能導致嚴重的心臟問題，甚至可能導致死亡。如果您發現心臟問題的症狀，例如呼吸急促或腳踝腫脹，請立即致電您的醫療保健提供者
- **血管（動脈）中血栓的問題：**若您有以下任何一種情況，請立即尋求緊急醫療援助：嚴重胸痛或壓迫感；手臂、背部、頸部或下顎疼痛；呼吸急促；身體一側麻痺或無力；說話有困難；突發性劇烈頭痛；視力突然改變

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。

LENVIMA已經證實有效。

LENVIMA的臨牀試驗，研究了954位無法進行手術的HCC患者，接受LENVIMA治療的患者數目為478，而接受sorafenib治療的患者數目為476人。在此試驗中，病人被隨機分配接受LENVIMA或sorafenib治療。結果表明，就整體生存期而言，與sorafenib相比，LENVIMA的治療效果不差於sorafenib（並非令人無法接受的差劣）。

接受LENVIMA治療的患者，其生存期的中位數為**13.6個月**，而接受sorafenib治療的患者其生存期中位數為12.3個月。中位數時間介於患者生存的最短和最長時間之間；與中位數時間相比，一半的患者壽命更長，而一半的患者壽命則較短。

接受LENVIMA治療的患者病情沒有惡化的生存的時間比接受sorafenib治療的患者延長了**兩倍** — 其中位數為7.3個月，sorafenib的則為3.6個月。

中位數是從最低到最高排列的數字列表中的中間數字。



接受LENVIMA治療的患者中見腫瘤縮小的比例(**41%**) 是接受sorafenib治療的患者中見腫瘤縮小的比例 (12%) 的3.5倍左右。

在LENVIMA組別中，10例患者 (2.1%) 沒有發現疾病徵兆，相比sorafenib組別中見的4例患者 (0.8%)。在LENVIMA組別中，184例患者 (38.5%) 顯出一些疾病徵兆，相比sorafenib組別中見的55例患者 (11.6%)。

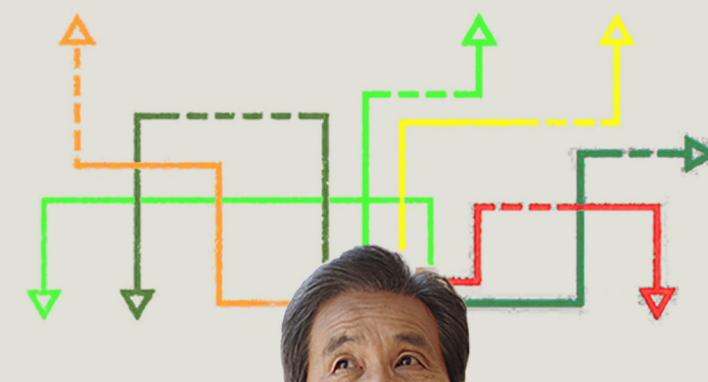


此試驗證明，LENVIMA作為第一線治療，可使某些無法進行手術的肝細胞癌患者受益。



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服用LENVIMA之前



服用LENVIMA之前，請先諮詢您的醫生。

若您的醫生讓您服用LENVIMA，您需要先與他/她討論一些事情。



以下是一些有助於您與醫生開始進行對話的問題。



在您服用LENVIMA前：

- 列出並描述當前的任何醫療健康狀況
- 如果您已懷孕，計劃懷孕或能夠懷孕，請告知您的醫生
- 列出您正在服用的任何草藥補品，維生素和其它藥物
- 尤其要告訴醫生您是否正在服用或服用過骨質疏鬆症藥物

- 怎樣知道LENVIMA是否適合我？
- 我應如何服用LENVIMA？
- 我應於何時覆診，以檢查進度？
- 服用LENVIMA可能會產生什麼副作用？
- 我應在什麼時候與您談及我可能遇到的副作用？
- 怎麼知道我是否能支付LENVIMA？

部分重要安全資訊

LENVIMA可能會引起嚴重的副作用，包括（續）：

- **肝臟問題：**LENVIMA可能引起肝臟問題，而且可導致肝功能衰竭和死亡。醫療保健提供者將在您使用LENVIMA治療前和治療期間，檢查您的肝功能。若您有以下任何症狀，請即告知您的醫療保健提供者：皮膚或眼白部分變黃（黃疸）；尿液呈深「茶色」；大便（糞便）呈淺色；感到昏昏欲睡、困惑或失去知覺

服用 LENVIMA



膠囊不顯示實際大小

要充分地利利用LENVIMA治療，正確服用和存放膠囊非常重要。

完全遵照醫生的處方服用 LENVIMA膠囊。



- 您的醫生會告訴您服用多少 LENVIMA，及於何時服用
- 完全遵照醫生處方，正確服用此藥物，十分重要
- 您的醫生可能會更改您服用 LENVIMA 的方式，例如：
 - 在治療期間，醫生處方的 LENVIMA 膠囊數量可能會遞減
 - 您的治療可能會停止一段時間
 - 如果發生某些副作用，您的治療可能會被完全終止
- 醫生將根據您的體重，決定您服用多少粒膠囊。您的起始劑量可能是每天兩粒或三粒，每粒膠囊4毫克。如果您的體重為60公斤（132磅）或以上，醫生可能會在開始時，讓您每天服用3粒 LENVIMA 膠囊。如果您的體重不足60公斤（132磅），醫生可能會在開始時讓您每天服用兩粒 LENVIMA 膠囊

欲了解更多有關如何服用
LENVIMA的信息，請訪問
www.OurLenvima.com/take-chinese

您可以隨餐或者空腹服用LENVIMA。

您可隨餐或空腹服用 LENVIMA，因此請選擇最方便自己的時間；應於每天同一時間服用。

若您不能吞下整顆 LENVIMA 膠囊，如何服用？



1. 將每日劑量（最多 5 粒）放入小容器或口服注射器（約 20 mL 容量）中
2. 將三毫升的水或蘋果汁加入容器或口服注射器中
3. 等待 10 分鐘，讓膠囊殼（外表面）完全溶解，然後攪拌或搖動混合物 3 分鐘，直到膠囊完全溶解。不要打破或壓碎膠囊
4. 飲用液體混合物或使用口腔注射器直接吸入口中
5. 接下來，使用第二個注射器，將額外的 2 mL 液體添加到容器或口服注射器中（在添加額外的水之前將第一個口服注射器蓋上蓋子），旋轉或搖晃並飲用混合液體
6. 重复此步骤至少一次，直到您看不到容器或口腔注射器中残留的任何 LENVIMA 混合物，以确保服用完所有药物

如果您的每日劑量需要 6 粒膠囊，請按照上述說明一次使用 3 粒膠囊。

LENVIMA 混合物可以在 36°F 至 46°F (2°C 至 8°C) 的冰箱中的有蓋容器中儲存最多 24 小時。如果在混合後 24 小時內未使用，請丟棄。

如何通過飼管給予 LENVIMA



如果 LENVIMA 飼管中給藥，應使用至少 5 French 直徑（聚氯乙烯或聚氨酯管）和至少 6 French 直徑（矽膠管）的飼管。

1. 將每日劑量（最多 5 粒）放入小容器或口服注射器（約 20 mL 容量）中
2. 向注射器中加入 3 mL 水。等待 10 分鐘，讓膠囊殼（外表面）完全溶解，然後攪拌或搖動混合物 3 分鐘，直到膠囊完全溶解。不要打破或壓碎膠囊
3. 通過導管將混合物服下
4. 接下來，蓋上注射器並取下柱塞。使用第二個注射器並向注射器中添加額外的 2 mL 液體。旋轉或搖動並將混合物放入進料管中。至少重複此步驟一次，直到看不到注射器中殘留的任何 LENVIMA 混合物，以確保服用完所有藥物

如果您的每日劑量需要 6 粒膠囊，請按照上述說明一次使用 3 粒膠囊。

混合物可以在 36°F 至 46°F (2°C 至 8°C) 的冰箱中的有蓋容器中儲存最多 24 小時。如果在混合後 24 小時內未使用，請丟棄。

LENVIMA 應於每天同一 時間服用一次。



設置提醒，在每天同一時間，服用一次醫生處方的相同劑量的 LENVIMA。譬如，您可以選定每天早上醒來時，或者每天晚上睡前，服用 LENVIMA 膠囊。

重要的是，每天，天天都要在同一時間服用，直到您的醫生決定做出更改為止。

若您錯過服用時間，怎麼辦？

- 若錯過服用 LENVIMA 不超過 12 小時，請於記起時盡快服用
- 若您若在 12 小時後才記起錯過了服用劑量，請不要服用，您可於下一既定時間服用下一劑

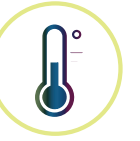
如您認為自己服用了過量的 LENVIMA，怎麼辦？



若您認為自己服用了過量的 LENVIMA 膠囊，請您：

- 立即致電您的醫生
或者
- 立即前往就近的醫院急診室

您應該如何存儲或保存 LENVIMA？



將 LENVIMA（和所有藥物）存放在兒童觸不到的安全地方，這一點十分重要。將室內溫度穩定在 68–77°F (20–25°C) 之間為最佳。

切勿以醫生處方以外的任何方式使用 LENVIMA。

除指定的處方外，切勿在其它情況服用 LENVIMA。即使別人有與您相同的症狀，切勿不要給別人 LENVIMA，因為此舉可能會傷害他人。若您需要有關 LENVIMA 的更多資訊，可向您的醫生或藥劑師查詢。

請參閱病人手冊中的部分重要安全資訊和 10-13 頁的內容以及隨同的完整處方信息。

處理治療的副作用

當您服用LENVIMA時，可能會有副作用，而且有些可能很嚴重。跟您的醫生討論任何您遇到的副作用是非常重要的。

有些行動可以幫助處理LENVIMA的副作用。您的醫生可助您選擇最適合的方法。重要的是，您身體上任何的變化，不管是否與治療有關，都要告訴醫生。

嚴重的副作用

據信，LENVIMA發揮作用的方式不僅影響癌細胞，還可以影響正常細胞，而且可能會導致嚴重的副作用。若出現任何症狀或症狀加劇，請立即致電或約見醫生：

高血壓（高血壓）

一個LENVIMA的常見副作用，且可能很嚴重。

- 在開始服用LENVIMA前，您的血壓首先應得到良好的控制
- 醫生應在您使用LENVIMA治療期間，定期檢查您的血壓。若血壓出現問題，您的醫生可能會給您開處方藥物治療高血壓

心臟問題

LENVIMA可能引起嚴重的心臟問題，並可導致死亡。若您有類似以下的心臟病症狀，請立即致電醫生：

- 呼吸急促
- 腳踝腫脹

血管（動脈）中血栓的問題

您若有以下任何一種情況，請立即尋求緊急醫療援助：

- 嚴重的胸痛或壓迫感
- 手臂、背部、頸部或下顎疼痛
- 呼吸急促
- 身體一側麻痺或無力
- 說話有困難
- 突發性劇烈頭痛
- 視力突然改變

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。

肝臟問題

LENVIMA可能引起肝臟問題，可能導致肝功能衰竭和死亡。

- 在使用LENVIMA治療前和治療期間，您的醫生會檢查您的肝功能
- 若您有以下任何症狀，請立即告訴醫生：
 - 您的皮膚或眼睛白色部分變黃（黃疸）
 - 尿液呈深「茶色」
 - 大便（糞便）呈淺色
 - 感到昏昏欲睡、困惑或失去知覺

腎臟問題

在LENVIMA治療中曾發生腎衰竭。腎衰竭可導致死亡。

- 醫生應定期替您驗血檢查腎臟

尿液中的蛋白質增加（蛋白尿）

這是服用LENVIMA常見的副作用，並且可能會很嚴重。蛋白尿是指尿液中的蛋白質增加。

- 在使用LENVIMA治療前和治療期間，醫生會檢查您尿液中蛋白質的含量

腹瀉

腹瀉是服用LENVIMA的一個常見副作用，並且可能會很嚴重。

- 若發生腹瀉，請向醫生查詢可以服用哪些藥物來治療腹瀉
- 腹瀉時多喝水是十分重要的
- 若您不能喝足夠的液體，並且無法控制腹瀉，請告知您的醫生或前往急診室

胃壁或腸壁上的開口（穿孔），或兩處或多處身體部位（瘻管）之間的異常連接

- 若發生嚴重的胃部（腹部）疼痛，請立即尋求緊急醫療救助

心臟電流活動的變化（QT延長）

QT延長會導致心跳不規則，且可危及生命

- 醫生將在您使用LENVIMA治療前和期間替您驗血，以檢查血液中鉀、鎂和鈣的水平，並可能通過ECG檢查您心臟的電流活動





LENVIMA可能會引起嚴重的副作用，包括 (續)：

血鈣水平低 (低血鈣症)

- 在LENVIMA治療期間，您的醫生將檢查您的血鈣水平
- 若您的鈣水平過低，醫生可能會告訴您服用鈣補充劑

一種稱為可逆性後腦白質腦病綜合症 (RPLS) 的疾病

若發現以下情況，請立即致電醫生：

- 劇烈頭痛
- 癲癇發作
- 無力
- 困惑
- 失明或視力改變

出血

LENVIMA可能引起嚴重的出血問題，甚至可能導致死亡。

若在使用LENVIMA治療期間，有任何出血的徵兆或症狀，請告知您的醫生，包括：

- 嚴重且持續的流鼻血
- 吐血

- 紅或黑色 (類似焦油) 的糞便
- 尿液帶血
- 咳出血或血凝塊
- 重度或新發的陰道出血

甲狀腺激素水平變化

- 醫生應在您開始使用LENVIMA前，以及在治療期間，每月替您檢查甲狀腺激素水平

傷口癒合問題

服用LENVIMA的人中，曾發生傷口癒合問題。

- 若計劃在LENVIMA治療前或期間進行任何手術，請告知您的醫生
- 您應在已預定的手術至少一週前，停止服用LENVIMA
- 您的醫生應該告訴您，手術後何時可再次開始服用LENVIMA

嚴重的顎骨問題 (也稱為骨壞死)

一些服用LENVIMA的患者曾發生過嚴重的顎骨問題。

- 某些風險因素可能會增加患上顎骨問題的風險，例如：
 - 服用 bisphosphonate 類藥物或 denosumab 藥物
 - 患有牙齒疾病
 - 侵入性牙科程序

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。

- 在開始使用LENVIMA之前以及治療期間，您的醫生應檢查您的口腔。重要的是要告訴您的牙醫，您正在服用LENVIMA，並且在服用LENVIMA時要維持良好的口腔護理
- 立即告訴您的醫生：
 - 在LENVIMA治療期間，如果您有任何顎骨問題的徵兆或症狀，包括顎骨疼痛，牙痛或牙齦潰瘍
 - 如果您打算在LENVIMA治療之前或期間進行任何牙科程序，您應該在預計的牙科手術或侵入性牙科程序之前至少 1 週停止服用LENVIMA。您的醫生應告訴您何時恢復服用LENVIMA。如果可能的話，在使用LENVIMA治療期間，應避免進行侵入性牙科程序。在進行侵入性牙科程序之前，停止使用 bisphosphonate 類藥物可能會降低患上顎骨問題的風險

常見副作用

LENVIMA在治療肝癌患者中最常見的副作用包括疲勞、食慾下降、關節和肌肉疼痛、體重減輕、胃部 (腹部) 疼痛、皮疹、發紅、瘙癢、手足皮膚剝落、聲音嘶啞、出血、甲狀腺激素水平變化和噁心。

LENVIMA可導致男性和女性的生育問題，亦可能會對您未出生的嬰兒產生危害。

請告知您的醫療保健提供者，您是否：

- 已懷孕或在計劃懷孕中。對於有可能懷孕的女性，您的醫生應該在您開始使用LENVIMA治療之前進行妊娠試驗。在接受LENVIMA治療期間，及最後一次服用LENVIMA後30天內，應使用有效的節育方法

- 正在哺餵母乳或計劃哺餵母乳。現尚未得知LENVIMA是否會進入母乳。在使用LENVIMA治療期間，以及最後一次服藥後一週內，不要哺餵母乳

如果您有某些副作用，您的醫療保健提供者可能需要減少LENVIMA的劑量，或延遲或完全停止治療。

這些並非LENVIMA所有的，可能出現的副作用。請致電您的醫生，徵求有關副作用的醫療建議。您可致電1-800-FDA-1088向FDA報告副作用，或訪問www.fda.gov/medwatch

常見副作用症狀的處理

服用LENVIMA時，您和您的醫生都可以採取一些措施來處理各種最常見的症狀。若您在服用LENVIMA時發生任何副作用，或副作用情況加劇，請務必立即聯絡您的醫生。

欲了解更多有關處理這些副作用的症狀的詳細信息和建議，請訪問 www.OurLenvima.com/side-chinese



幫助支付 LENVIMA



獲取 LENVIMA



膠囊不顯示實際大小

若您和醫生一致決定LENVIMA是適合您的藥物，Eisai會提供對您可能有的幫助的資源。

符合條件的患者可能會得到援助：



- 沒有醫保的患者
- 不知自己是否能支付膠囊費用的患者
- 不知自己是否能支付保險共付額的患者

Eisai的援助計劃

- 了解您的醫保可能如何承保您的治療*
- 了解更多有關治療的自付費用的資訊
- 如果您不能支付藥物相關的費用，看看您是否符合援助計劃的要求

 THE EISAI
ASSISTANCE
PROGRAM

電話：1-866-61-EISAI (1-866-613-4724)

傳真：1-855-246-5192

時間：週一至週五，
美國東部時間上午8時至晚上8時

www.LenvimaReimbursement.com

請注意：以下是英語網站鏈接。
所提供的電話號碼均由講英語的
代表接聽。如有需要，他們可以根
據您選擇的語言提供口譯服務。



您可以通過以下方式獲得 LENVIMA：

- 某些專業藥房
- 選擇符合資格的醫生辦公室或診所
- 選擇符合資格的醫院藥房

專業藥房

- LENVIMA 可通過某些專業藥房獲得，這些藥房會將藥物直接郵寄給患者。請訪問 www.LenvimaSpecialtyPharmacy.com 獲取分配 LENVIMA 的郵購專業藥房的完整列表

醫師辦公室/診所或醫院藥房

- LENVIMA 也可以通過符合條件的醫生辦公室、診所或醫院藥房配藥。請聯繫您首選的經銷商以獲取更多信息，包括資格要求



欲了解更多有關如何獲取LENVIMA
的信息，請訪問

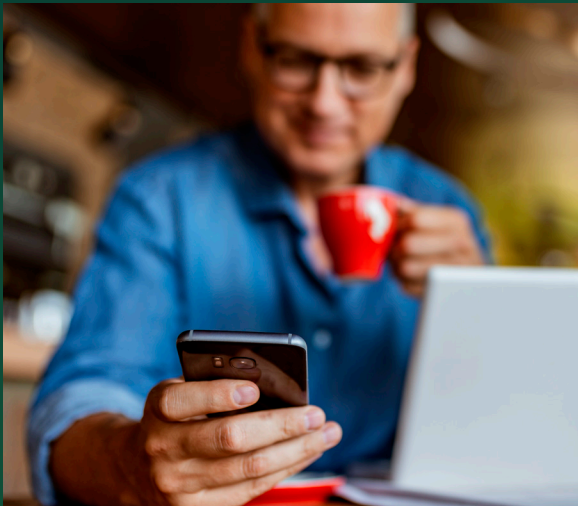
www.OurLenvima.com/access-chinese

*Eisai不能保證任何醫保理賠付款。編碼、承保範圍和報銷金額可能因支付者、計劃、病人和護理的設定而出現重大差異。實際的承保範圍和報銷決定均由各支付方在收到理賠收據後作出。如需更多資料，顧客應諮詢其支付單位，以了解所有相關編碼、報銷及承保範圍的要求。選擇適當的編碼，並確保所有理賠和報銷上的準確性等皆由醫療提供者完全負責。所有服務必須是醫學上合適，並在患者病歷中有適當的支持。

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。

請注意，一些專業藥房提供的電話可能配有會說您首選語言的口譯員，請向說英語的工作人員要求口譯員服務。





訪問
www.OurLenvima.com/chinese
網站, 了解更多信息

鼓勵您向FDA報告處方藥的不良副作用。

請訪問www.fda.gov/medwatch或致電1-800-FDA-1088。

CHINESE

請參閱病人手冊中的部分重要安全資訊和10-13頁的內容以及隨同的完整處方信息。



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LENVIMA safely and effectively. See full prescribing information for LENVIMA.

LENVIMA® (lenvatinib) capsules, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.4)	08/2022
Dosage and Administration (2.1)	08/2022
Dosage and Administration (2.10)	11/2022

INDICATIONS AND USAGE

LENVIMA is a kinase inhibitor that is indicated:

Differentiated Thyroid Cancer (DTC)

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). (1.1)

Renal Cell Carcinoma (RCC)

- In combination with pembrolizumab, for the first line treatment of adult patients with advanced renal cell carcinoma (RCC). (1.2)
- In combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. (1.2)

Hepatocellular Carcinoma (HCC)

- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). (1.3)

Endometrial Carcinoma (EC)

- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.4, 2.1)

DOSAGE AND ADMINISTRATION

Single Agent Therapy:

- DTC: The recommended dosage is 24 mg orally once daily. (2.3)
- HCC: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg. (2.5)

Combination Therapy:

- EC: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. (2.6)
- RCC: The recommended dosage is:
 - 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. (2.4)
 - 18 mg orally once daily with everolimus 5 mg orally once daily. (2.4)

Modify the recommended daily dose for certain patients with renal or hepatic impairment. (2.8, 2.9)

DOSAGE FORMS AND STRENGTHS

Capsules: 4 mg and 10 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypertension:** Control blood pressure prior to treatment and monitor during treatment. Withhold for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for Grade 4 hypertension. (2.7, 5.1)
- Cardiac Dysfunction:** Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold or discontinue for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction. (2.7, 5.2)
- Arterial Thromboembolic Events:** Discontinue following an arterial thromboembolic event. (2.7, 5.3)
- Hepatotoxicity:** Monitor liver function prior to treatment and periodically during treatment. Withhold or discontinue for Grade 3 or 4 hepatotoxicity. Discontinue for hepatic failure. (2.7, 5.4)
- Renal Failure or Impairment:** Withhold or discontinue for Grade 3 or 4 renal failure or impairment. (2.7, 5.5)

- Proteinuria:** Monitor for proteinuria prior to treatment and periodically during treatment. Withhold for 2 or more grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome. (2.7, 5.6)
- Diarrhea:** May be severe and recurrent. Promptly initiate management for severe diarrhea. Withhold or discontinue based on severity. (2.7, 5.7)
- Fistula Formation and Gastrointestinal Perforation:** Discontinue in patients who develop Grade 3 or 4 fistula or any Grade gastrointestinal perforation. (2.7, 5.8)
- QT Interval Prolongation:** Monitor and correct electrolyte abnormalities. Withhold for QT interval greater than 500 ms or for 60 ms or greater increase in baseline QT interval. (2.7, 5.9)
- Hypocalcemia:** Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold or discontinue based on severity. (2.7, 5.10)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Withhold for RPLS until fully resolved or discontinue. (2.7, 5.11)
- Hemorrhagic Events:** Withhold or discontinue based on severity. (2.7, 5.12)
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction:** Monitor thyroid function prior to treatment and monthly during treatment. (5.13)
- Impaired Wound Healing:** Withhold LENVIMA for at least 1 week before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established. (5.14)
- Osteonecrosis of the Jaw:** Consider preventive dentistry prior to treatment with LENVIMA. Avoid invasive dental procedures, if possible, particularly in patients at higher risk. (5.15)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.16, 8.1, 8.3)

ADVERSE REACTIONS

- In DTC, the most common adverse reactions (incidence $\geq 30\%$) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. (6.1)
 - In RCC:
 - The most common adverse reactions (incidence $\geq 20\%$) for LENVIMA and pembrolizumab are fatigue, diarrhea, musculoskeletal pain, hypothyroidism, hypertension, stomatitis, decreased appetite, rash, nausea, decreased weight, dysphonia, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, hemorrhagic events, vomiting, constipation, hepatotoxicity, headache, and acute kidney injury. (6.1)
 - The most common adverse reactions (incidence $\geq 30\%$) for LENVIMA and everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. (6.1)
 - In HCC, the most common adverse reactions (incidence $\geq 20\%$) for LENVIMA are hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. (6.1)
 - In EC, the most common adverse reactions (incidence $\geq 20\%$) for LENVIMA and pembrolizumab are hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, decreased weight, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, and rash. (6.1)
- To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-877-873-4724 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Differentiated Thyroid Cancer

LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

1.2 Renal Cell Carcinoma

LENVIMA, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

LENVIMA, in combination with everolimus, is indicated for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy.

1.3 Hepatocellular Carcinoma

LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

1.4 Endometrial Carcinoma

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation [see *Dosage and Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with LENVIMA in combination with pembrolizumab based on MSI or MMR status in tumor specimens [see *Clinical Studies (14.4)*].

Information on FDA-approved tests for patient selection is available at: <http://www.fda.gov/CompanionDiagnostics>.

An FDA-approved test for the selection of patients who are not MSI-H is not currently available.

2.2 Important Dosage Information

- Reduce the dose for certain patients with renal or hepatic impairment [see *Dosage and Administration (2.8, 2.9)*].
- Take LENVIMA once daily, with or without food, at the same time each day [see *Clinical Pharmacology (12.3)*]. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

2.3 Recommended Dosage for Differentiated Thyroid Cancer (DTC)

The recommended dosage of LENVIMA is 24 mg orally once daily until disease progression or until unacceptable toxicity.

2.4 Recommended Dosage for Renal Cell Carcinoma (RCC)

First-Line Treatment of Patients with Advanced RCC

The recommended dosage of LENVIMA is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or until unacceptable toxicity or up to 2 years. After completing 2 years of combination therapy, LENVIMA may be administered as a single agent until disease progression or until unacceptable toxicity.

Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

Previously Treated RCC

The recommended dosage of LENVIMA is 18 mg in combination with 5 mg everolimus orally once daily until disease progression or until unacceptable toxicity.

Refer to the everolimus prescribing information for recommended everolimus dosing information.

2.5 Recommended Dosage for Hepatocellular Carcinoma (HCC)

The recommended dosage of LENVIMA is based on actual body weight:

- 12 mg for patients greater than or equal to 60 kg or
- 8 mg for patients less than 60 kg.

Take LENVIMA orally once daily until disease progression or until unacceptable toxicity.

2.6 Recommended Dosage for Endometrial Carcinoma (EC)

The recommended dosage of LENVIMA is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression.

Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

2.7 Dosage Modifications for Adverse Reactions

Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of LENVIMA for adverse reactions.

Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions		
Adverse Reaction	Severity^a	Dosage Modifications for LENVIMA
Hypertension [<i>see Warnings and Precautions (5.1)</i>]	Grade 3	<ul style="list-style-type: none">• Withhold for Grade 3 that persists despite optimal antihypertensive therapy.• Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	<ul style="list-style-type: none">• Permanently discontinue.
	Grade 3	<ul style="list-style-type: none">• Withhold until improves to Grade 0 to 1 or baseline.

Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	Severity^a	Dosage Modifications for LENVIMA
Cardiac Dysfunction [<i>see Warnings and Precautions (5.2)</i>]		<ul style="list-style-type: none">Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	<ul style="list-style-type: none">Permanently discontinue.
Arterial Thromboembolic Event [<i>see Warnings and Precautions (5.3)</i>]	Any Grade	<ul style="list-style-type: none">Permanently discontinue.
Hepatotoxicity [<i>see Warnings and Precautions (5.4)</i>]	Grade 3 or 4	<ul style="list-style-type: none">Withhold until improves to Grade 0 to 1 or baseline.Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity.Permanently discontinue for hepatic failure.
Renal Failure or Impairment [<i>see Warnings and Precautions (5.5)</i>]	Grade 3 or 4	<ul style="list-style-type: none">Withhold until improves to Grade 0 to 1 or baseline.Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria [<i>see Warnings and Precautions (5.6)</i>]	2 g or greater proteinuria in 24 hours	<ul style="list-style-type: none">Withhold until less than or equal to 2 grams of proteinuria per 24 hours.Resume at a reduced dose.Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation [<i>see Warnings and Precautions (5.8)</i>]	Any Grade	<ul style="list-style-type: none">Permanently discontinue.
Fistula Formation [<i>see Warnings and Precautions (5.8)</i>]	Grade 3 or 4	<ul style="list-style-type: none">Permanently discontinue.
QT Prolongation [<i>see Warnings and Precautions (5.9)</i>]	Greater than 500 ms or greater than 60 ms increase from baseline	<ul style="list-style-type: none">Withhold until improves to less than or equal to 480 ms or baseline.Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy	Any Grade	<ul style="list-style-type: none">Withhold until fully resolved.

Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions		
Adverse Reaction	Severity^a	Dosage Modifications for LENVIMA
Syndrome [see Warnings and Precautions (5.11)]		<ul style="list-style-type: none"> Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions [see Warnings and Precautions (5.7, 5.10, 5.12)]	Persistent or intolerable Grade 2 or 3 adverse reaction	<ul style="list-style-type: none"> Withhold until improves to Grade 0 to 1 or baseline. Resume at reduced dose.
	Grade 4 laboratory abnormality	
	Grade 4 adverse reaction	<ul style="list-style-type: none"> Permanently discontinue.

^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Table 2: Recommended Dosage Reductions of LENVIMA for Adverse Reactions			
Indication	First Dosage Reduction To	Second Dosage Reduction To	Third Dosage Reduction To
DTC	20 mg once daily	14 mg once daily	10 mg once daily
RCC	14 mg once daily	10 mg once daily	8 mg once daily
Endometrial Carcinoma	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
<ul style="list-style-type: none"> Actual weight 60 kg or greater 	8 mg once daily	4 mg once daily	4 mg every other day
<ul style="list-style-type: none"> Actual weight less than 60 kg 	4 mg once daily	4 mg every other day	Discontinue

Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Pembrolizumab

When administering LENVIMA in combination with pembrolizumab, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in Table 1. Refer to pembrolizumab prescribing information for additional dose modification information.

Recommended Dose Modifications for Adverse Reactions for LENVIMA in Combination with Everolimus

When administering LENVIMA in combination with everolimus, withhold or reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

2.8 Dosage Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is [*see Warnings and Precautions (5.5), Use in Specific Populations (8.6)*]:

- Differentiated thyroid cancer: 14 mg orally once daily
- Renal cell carcinoma: 10 mg orally once daily
- Endometrial carcinoma: 10 mg orally once daily

2.9 Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is [*see Warnings and Precautions (5.4), Use in Specific Populations (8.7)*]:

- Differentiated thyroid cancer: 14 mg taken orally once daily
- Renal cell carcinoma: 10 mg taken orally once daily
- Endometrial carcinoma: 10 mg orally once daily

2.10 Capsule Administration and Preparation of Suspension for Administration

Administration

Oral: Capsule or Suspension

Capsule

- Swallow LENVIMA capsules whole at the same time each day with or without food [*see Clinical Pharmacology (12.3)*].

Suspension

- Prepare [*see Preparation below*] oral suspension with water or apple juice and administer at the same time each day with or without food [*see Clinical Pharmacology (12.3)*].

Feeding Tube Administration

Suspension

- Prepare [*see Preparation below*] suspension for feeding tube administration with water and administer at the same time each day with or without food [*see Clinical Pharmacology (12.3)*].

Preparation of Suspension

- Place the required number of capsules, up to a maximum of 5, in a small container (approximately 20 mL capacity) or syringe (20 mL). Do not break or crush capsules.
- Add 3 mL of liquid to the container or syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until capsules are fully disintegrated and administer the entire contents.
- Next, add an additional 2 mL of liquid to the container or syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least once and until there is no visible residue to ensure all of the medication is taken.
- If 6 capsules are required for a dose, follow these instructions using 3 capsules at a time.

If LENVIMA suspension is not used at the time of preparation, LENVIMA suspension may be stored in a refrigerator at 36°F to 46°F (2°C to 8°C) for a maximum of 24 hours in a covered container. If not administered within 24 hours, the suspension should be discarded.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 4 mg: yellowish-red body and yellowish-red cap, marked in black ink with “C” on cap and “LENV 4 mg” on body.
- 10 mg: yellow body and yellowish-red cap, marked in black ink with “C” on cap and “LENV 10 mg” on body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.

In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure ≥ 160 mmHg occurred in 29% of patients and diastolic blood pressure ≥ 100 mmHg occurred in 21% [*see Adverse Reactions (6.1)*].

Serious complications of poorly controlled hypertension have been reported.

Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity [see *Dosage and Administration (2.7)*].

5.2 Cardiac Dysfunction

Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC or HCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of LENVIMA-treated patients.

Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity [see *Dosage and Administration (2.7)*].

5.3 Arterial Thromboembolic Events

Among patients receiving LENVIMA or LENVIMA with everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in Study 205 (RCC), 2% of patients in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials [see *Adverse Reactions (6.1)*].

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue LENVIMA following an arterial thrombotic event [see *Dosage and Administration (2.7)*]. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

5.4 Hepatotoxicity

Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients.

In REFLECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of LENVIMA-treated patients and 2% of sorafenib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Two percent of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to hepatic encephalopathy and 1% of patients discontinued lenvatinib or sorafenib due to hepatic failure [see *Adverse Reactions (6.1)*].

Monitor liver function prior to initiating LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a

reduced dose upon recovery or permanently discontinue LENVIMA based on severity [*see Dosage and Administration (2.7)*].

5.5 Renal Failure or Impairment

Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study.

In Study 205 (RCC), renal impairment or renal failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients [*see Adverse Reactions (6.1)*].

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA for renal failure or impairment based on severity [*see Dosage and Administration (2.7)*].

5.6 Proteinuria

Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus [*see Adverse Reactions (6.1)*].

Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity [*see Dosage and Administration (2.7)*].

5.7 Diarrhea

Of the 737 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diarrhea occurred in 49% of patients, including Grade 3 in 6%.

In Study 205 (RCC), diarrhea occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%. Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred despite dose reduction [*see Adverse Reactions (6.1)*].

Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity [*see Dosage and Administration (2.7)*].

5.8 Fistula Formation and Gastrointestinal Perforation

Of 799 patients treated with LENVIMA or LENVIMA with everolimus in SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), fistula or gastrointestinal perforation occurred in 2%.

Permanently discontinue LENVIMA in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula [*see Dosage and Administration (2.7)*].

5.9 QT Interval Prolongation

In SELECT (DTC), QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In Study 205 (RCC), QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval >500 ms occurred in 6%. In REFLECT (HCC), QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose of LENVIMA upon recovery based on severity [see *Dosage and Administration (2.7)*].

5.10 Hypocalcemia

In SELECT (DTC), Grade 3 to 4 hypocalcemia occurred in 9% of patients receiving LENVIMA. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation, with or without dose interruption or dose reduction.

In Study 205 (RCC), Grade 3 to 4 hypocalcemia occurred in 6% of patients treated with LENVIMA with everolimus. In REFLECT (HCC), Grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients [see *Adverse Reactions (6.1)*].

Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA depending on severity [see *Dosage and Administration (2.7)*].

5.11 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies of 1823 patients who received LENVIMA as a single agent [see *Adverse Reactions (6.1)*], reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 0.3%.

Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA depending on severity and persistence of neurologic symptoms [see *Dosage and Administration (2.7)*].

5.12 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with LENVIMA. Across SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria.

In SELECT, Grade 3 to 5 hemorrhage occurred in 2% of patients receiving LENVIMA, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In Study 205, Grade 3 to 5 hemorrhage occurred in 8% of patients receiving LENVIMA with everolimus, including 1 fatal cerebral hemorrhage. In REFLECT, Grade 3 to 5 hemorrhage occurred in 5% of patients receiving LENVIMA, including 7 fatal hemorrhagic events [see *Adverse Reactions (6.1)*].

Serious tumor related bleeds, including fatal hemorrhagic events, occurred in patients treated with LENVIMA in clinical trials and in the post-marketing setting. In post-marketing

surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g. carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA based on the severity [*see Dosage and Administration (2.7)*].

5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

LENVIMA impairs exogenous thyroid suppression. In SELECT (DTC), 88% of all patients had a baseline thyroid stimulating hormone (TSH) level ≤ 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients.

Grade 1 or 2 hypothyroidism occurred in 24% of patients receiving LENVIMA with everolimus in Study 205 (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 70% of patients receiving LENVIMA in REFLECT and 60% of patients receiving LENVIMA with everolimus in Study 205 [*see Adverse Reactions (6.1)*].

Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

5.14 Impaired Wound Healing

Impaired wound healing has been reported in patients who received LENVIMA [*see Adverse Reactions (6.2)*].

Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

5.15 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving LENVIMA [*see Adverse Reactions (6.1)*]. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

5.16 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypertension [see *Warnings and Precautions* (5.1)]
- Cardiac Dysfunction [see *Warnings and Precautions* (5.2)]
- Arterial Thromboembolic Events [see *Warnings and Precautions* (5.3)]
- Hepatotoxicity [see *Warnings and Precautions* (5.4)]
- Renal Failure and Impairment [see *Warnings and Precautions* (5.5)]
- Proteinuria [see *Warnings and Precautions* (5.6)]
- Diarrhea [see *Warnings and Precautions* (5.7)]
- Fistula Formation and Gastrointestinal Perforation [see *Warnings and Precautions* (5.8)]
- QT Interval Prolongation [see *Warnings and Precautions* (5.9)]
- Hypocalcemia [see *Warnings and Precautions* (5.10)]
- Reversible Posterior Leukoencephalopathy Syndrome [see *Warnings and Precautions* (5.11)]
- Hemorrhagic Events [see *Warnings and Precautions* (5.12)]
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction [see *Warnings and Precautions* (5.13)]
- Impaired Wound Healing [see *Warnings and Precautions* (5.14)]
- Osteonecrosis of the Jaw (ONJ) [see *Warnings and Precautions* (5.15)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions reflect exposure to LENVIMA as a single agent in 261 patients with DTC (SELECT) and 476 patients with HCC (REFLECT), LENVIMA with pembrolizumab in 406 patients with endometrial carcinoma (Study 309), LENVIMA with everolimus in 62 patients with RCC (Study 205), and LENVIMA with pembrolizumab in 352 patients with RCC (CLEAR). Safety data obtained in 1823 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions. Among the 1823 patients who

received LENVIMA as a single agent, the median age was 61 years (20 to 89 years), the dose range was 0.2 mg to 32 mg daily, and the median duration of exposure was 5.6 months.

The data below reflect exposure to LENVIMA in 1557 patients enrolled in randomized, active-controlled trials (REFLECT; Study 205; CLEAR; Study 309), and a randomized, placebo-controlled trial (SELECT). The median duration of exposure to LENVIMA across these five studies ranged from 6 to 16 months. The demographic and exposure data for each clinical trial population are described in the subsections below.

Differentiated Thyroid Cancer

The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory differentiated thyroid cancer were randomized (2:1) to LENVIMA (n=261) or placebo (n=131) [see *Clinical Studies (14.1)*]. The median treatment duration was 16.1 months for LENVIMA. Among 261 patients who received LENVIMA, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black; and 4% were Hispanic/Latino.

The most common adverse reactions observed in LENVIMA-treated patients ($\geq 30\%$) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 3 presents adverse reactions occurring at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the study.

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular				
Hypertension ^a	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis ^b	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain ^c	31	2	11	1
Constipation	29	0.4	15	1
Oral pain ^d	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0

Table 3: Adverse Reactions Occurring in Patients with a Between-Group Difference of $\geq 5\%$ in All Grades or $\geq 2\%$ in Grades 3 and 4 in SELECT (DTC)

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue ^e	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^f	62	5	28	3
Metabolism and Nutrition				
Decreased appetite	54	7	18	1
Decreased weight	51	13	15	1
Dehydration	9	2	2	1
Nervous System				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash ^g	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric				
Insomnia	12	0	3	0
Infections				
Urinary tract infection	11	1	5	0
Dental and oral infections ^h	10	1	1	0
Cardiac				
Electrocardiogram QT prolonged	9	2	2	0
<p>a Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure</p> <p>b Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation</p> <p>c Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain</p> <p>d Includes oral pain, glossodynia, and oropharyngeal pain</p> <p>e Includes asthenia, fatigue, and malaise</p> <p>f Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia</p> <p>g Includes macular rash, maculo-papular rash, generalized rash, and rash</p> <p>h Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection</p>				

Clinically important adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of $< 5\%$ were pulmonary embolism (3%, including fatal reports vs 2%, respectively) and osteonecrosis of the jaw (0.4% vs 0%, respectively).

Laboratory abnormalities with a difference of $\geq 2\%$ in Grade 3 – 4 events and at a higher incidence in the LENVIMA arm are presented in Table 4.

Table 4: Laboratory Abnormalities with a Difference of $\geq 2\%$ in Grade 3 - 4 Events and at a Higher Incidence in the LENVIMA Arm^{a, b} in SELECT (DTC)		
Laboratory Abnormality	LENVIMA 24 mg	Placebo
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypocalcemia	9	2
Hypokalemia	6	1
Increased aspartate aminotransferase (AST)	5	0
Increased alanine aminotransferase (ALT)	4	0
Increased lipase	4	1
Increased creatinine	3	0
Hematology		
Thrombocytopenia	2	0
<p>a With at least 1 grade increase from baseline</p> <p>b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n = 253 to 258), Placebo (n = 129 to 131)</p>		

The following laboratory abnormalities (all Grades) occurred in $>5\%$ of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

First-Line Treatment of Renal Cell Carcinoma in Combination with Pembrolizumab (CLEAR)

The safety of LENVIMA in combination with pembrolizumab was investigated in CLEAR [see *Clinical Studies (14.2)*]. Patients received LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=352), or LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of LENVIMA and pembrolizumab was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA in combination with pembrolizumab, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in $\geq 2\%$ of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 37% of patients; 26% LENVIMA only, 29% pembrolizumab only, and 13% both drugs. The most common adverse reactions ($\geq 2\%$) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with pembrolizumab. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), and vomiting (6%), increased ALT (5%), and increased amylase (5%).

Tables 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in $\geq 20\%$ of patients treated with LENVIMA and pembrolizumab in CLEAR.

Table 5: Adverse Reactions in $\geq 20\%$ of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)				
	LENVIMA 20 mg in combination with Pembrolizumab 200mg N=352		Sunitinib 50 mg N=340	
Adverse Reactions	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
General				
Fatigue ^a	63	9	56	8
Gastrointestinal				
Diarrhea ^b	62	10	50	6
Stomatitis ^c	43	2	43	2
Nausea	36	3	33	1
Abdominal pain ^d	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and connective tissue				
Musculoskeletal pain ^e	58	4	41	3
Endocrine				
Hypothyroidism ^f	57	1	32	0
Vascular				
Hypertension ^g	56	29	43	20
Hemorrhagic events ^h	27	5	26	4
Metabolism				
Decreased appetite ⁱ	41	4	31	1

Table 5: Adverse Reactions in $\geq 20\%$ of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)				
	LENVIMA 20 mg in combination with Pembrolizumab 200mg N=352		Sunitinib 50 mg N=340	
Adverse Reactions	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue				
Rash ^l	37	5	17	1
Palmar-plantar erythrodysesthesia syndrome ^k	29	4	38	4
Respiratory, thoracic, and mediastinal				
Dysphonia	30	0	4	0
Renal and urinary				
Proteinuria ^l	30	8	13	3
Acute kidney injury ^m	21	5	16	2
Investigations				
Weight decreased	30	8	9	0
Hepatobiliary				
Hepatotoxicity ⁿ	25	9	21	5
Nervous system				
Headache	23	1	16	1
<p>a Includes asthenia, fatigue, lethargy and malaise</p> <p>b Includes diarrhea and gastroenteritis</p> <p>c Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis</p> <p>d Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain</p> <p>e Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and pain in jaw</p> <p>f Includes hypothyroidism, increased blood thyroid stimulating hormone and secondary hypothyroidism</p> <p>g Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure</p> <p>h Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include: Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemeses, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, and upper gastrointestinal hemorrhage</p> <p>i Includes decreased appetite and early satiety</p> <p>j Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular</p>				

	LENVIMA 20 mg in combination with Pembrolizumab 200mg N=352		Sunitinib 50 mg N=340	
Adverse Reactions	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
k	Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome and plantar erythema			
l	Includes hemoglobinuria, nephrotic syndrome, and proteinuria			
m	Includes acute kidney injury, azotaemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininaemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic			
n	Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, and gamma-glutamyltransferase increased			

Clinically relevant adverse reactions ($<20\%$) that occurred in patients receiving LENVIMA/pembrolizumab were myocardial infarction (3%) and angina pectoris (1%).

	LENVIMA 20 mg in combination with Pembrolizumab 200 mg		Sunitinib 50 mg	
Laboratory Abnormality^a	All Grades %^b	Grades 3-4 %^b	All Grades %^b	Grade 3-4 %^b
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased aspartate aminotransferase (AST)	58	7	57	3
Hyperglycemia	55	7	48	3
Increased alanine aminotransferase (ALT)	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0

Table 6: Laboratory Abnormalities in $\geq 20\%$ (All Grades) of Patients on LENVIMA plus Pembrolizumab in CLEAR (RCC)				
Laboratory Abnormality^a	LENVIMA 20 mg in combination with Pembrolizumab 200 mg		Sunitinib 50 mg	
	All Grades %^b	Grades 3-4 %^b	All Grades %^b	Grade 3-4 %^b
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16
a With at least 1 grade increase from baseline b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA/pembrolizumab (n= 343 to 349) and sunitinib (n= 329 to 335).				

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥ 2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥ 40 mg daily oral prednisone equivalent. Recurrence of Grade ≥ 2 increased ALT or AST was observed in 3 patients on rechallenge in patients receiving LENVIMA and 10 patients receiving both LENVIMA and pembrolizumab.

Previously Treated Renal Cell Carcinoma in Combination with Everolimus (Study 205)

The safety of LENVIMA was evaluated in Study 205, in which patients with unresectable advanced or metastatic renal cell carcinoma (RCC) were randomized (1:1:1) to LENVIMA 18 mg orally once daily with everolimus 5 mg orally once daily (n=51), LENVIMA 24 mg orally once daily (n=52), or everolimus 10 mg orally once daily (n=50) [see *Clinical Studies (14.2)*]. This data also includes patients on the dose escalation portion of the study who received LENVIMA with everolimus (n=11). The median treatment duration was 8.1 months for LENVIMA with everolimus. Among 62 patients who received LENVIMA with everolimus, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA with everolimus-treated group ($\geq 30\%$) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. The most common serious adverse reactions ($\geq 5\%$) were renal failure (11%),

dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA with everolimus. The most common adverse reactions ($\geq 5\%$) resulting in dose reductions in the LENVIMA with everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA with everolimus-treated group.

Table 7 presents the adverse reactions in $>15\%$ of patients in the LENVIMA with everolimus arm. Study 205 was not designed to demonstrate a statistically significant difference in adverse reaction rates for LENVIMA in combination with everolimus, as compared to everolimus for any specific adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in $>15\%$ of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)				
Adverse Reactions	LENVIMA 18 mg with Everolimus 5 mg N=62		Everolimus 10 mg N=50	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism	24	0	2	0
Gastrointestinal				
Diarrhea	81	19	34	2
Vomiting	48	7	12	0
Nausea	45	5	16	0
Stomatitis/Oral inflammation ^a	44	2	50	4
Abdominal pain ^b	37	3	8	0
Oral pain ^c	23	2	4	0
Dyspepsia/Gastro-esophageal reflux	21	0	12	0
Constipation	16	0	18	0
General				
Fatigue ^d	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Metabolism and Nutrition				
Decreased appetite	53	5	18	0
Decreased weight	34	3	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^e	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System				
Headache	19	2	10	2
Psychiatric				
Insomnia	16	2	2	0

Table 7: Adverse Reactions Occurring in >15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)				
	LENVIMA 18 mg with Everolimus 5 mg N=62		Everolimus 10 mg N=50	
Adverse Reactions	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Renal and Urinary				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event ^f	18	10	12	2
Respiratory, Thoracic and Mediastinal				
Cough	37	0	30	0
Dyspnea/Exertional dyspnea	35	5	28	8
Dysphonia	18	0	4	0
Skin and Subcutaneous Tissue				
Rash ^g	35	0	40	0
Vascular				
Hypertension/Increased blood pressure	42	13	10	2
Hemorrhagic events ^h	32	6	26	2
<p>a Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration</p> <p>b Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain</p> <p>c Includes gingival pain, glossodynia, and oropharyngeal pain</p> <p>d Includes asthenia, fatigue, lethargy and malaise</p> <p>e Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia</p> <p>f Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment</p> <p>g Includes erythema, erythematous rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, and septic rash</p> <p>h Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele</p>				

In Table 8, Grade 3-4 laboratory abnormalities occurring in $\geq 3\%$ of patients in the LENVIMA with everolimus arm are presented.

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 3\%$ of Patients in the LENVIMA with Everolimus Arm^{a,b} in Study 205 (RCC)		
Laboratory Abnormality	LENVIMA 18 mg with Everolimus 5 mg	Everolimus 10 mg
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypertriglyceridemia	18	18
Increased lipase	13	12
Hypercholesterolemia	11	0
Hyponatremia	11	6
Hypophosphatemia	11	6
Hyperkalemia	6	2
Hypocalcemia	6	2
Hypokalemia	6	2

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 3\%$ of Patients in the LENVIMA with Everolimus Arm^{a,b} in Study 205 (RCC)		
Laboratory Abnormality	LENVIMA 18 mg with Everolimus 5 mg	Everolimus 10 mg
	Grades 3-4 (%)	Grades 3-4 (%)
Increased aspartate aminotransferase (AST)	3	0
Increased alanine aminotransferase (ALT)	3	2
Increased alkaline phosphatase	3	0
Hyperglycemia	3	16
Increased creatine kinase	3	4
Hematology		
Lymphopenia	10	20
Anemia	8	16
Thrombocytopenia	5	0
a With at least 1 grade increase from baseline b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA with Everolimus (n = 62), Everolimus (n = 50).		

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=476) or sorafenib (n=475) [see *Clinical Studies (14.3)*]. The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥ 60 kg and 8 mg orally once daily for patients with a baseline body weight of < 60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was ≥ 6 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients ($\geq 20\%$) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

The most common serious adverse reactions ($\geq 2\%$) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%).

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Table 9 summarizes the adverse reactions that occurred in $\geq 10\%$ of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 9.

Table 9: Adverse Reactions Occurring in $\geq 10\%$ of Patients in the LENVIMA Arm in REFLECT (HCC)				
Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism ^a	21	0	3	0
Gastrointestinal				
Diarrhea	39	4	46	4
Abdominal pain ^b	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites ^c	15	4	11	3
Stomatitis ^d	11	0.4	14	1
General				
Fatigue ^e	44	7	36	6
Pyrexia ^f	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Metabolism and Nutrition				
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^g	31	1	20	2
Nervous System				
Headache	10	1	8	0
Renal and Urinary				
Proteinuria ^h	26	6	12	2
Respiratory, Thoracic and Mediastinal				
Dysphonia	24	0.2	12	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	27	3	52	11
Rash ⁱ	14	0	24	2
Vascular				
Hypertension ^j	45	24	31	15
Hemorrhagic events ^k	23	4	15	4
<p>a Includes hypothyroidism, blood thyroid stimulating hormone increased.</p> <p>b Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain</p> <p>c Includes ascites and malignant ascites</p>				

Table 9: Adverse Reactions Occurring in $\geq 10\%$ of Patients in the LENVIMA Arm in REFLECT (HCC)				
Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
d	Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis			
e	Includes asthenia, fatigue, lethargy and malaise			
f	Includes increased body temperature, pyrexia			
g	Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia			
h	Includes proteinuria, increased urine protein, protein urine present			
i	Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and rash			
j	Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension			
k	Includes all hemorrhage terms. Hemorrhage terms that occurred in 5 or more subjects in either treatment group include: epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal varices hemorrhage, hemorrhoidal hemorrhage, mouth hemorrhage, rectal hemorrhage and upper gastrointestinal hemorrhage			

In Table 10, Grade 3-4 laboratory abnormalities occurring in $\geq 2\%$ of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 10: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 2\%$ of Patients in the LENVIMA Arm^{a,b} in REFLECT (HCC)		
Laboratory Abnormality	Lenvatinib (%)	Sorafenib (%)
Chemistry		
Increased GGT	17	20
Hyponatremia	15	9
Hyperbilirubinemia	13	10
Increased aspartate aminotransferase (AST)	12	18
Increased alanine aminotransferase (ALT)	8	9
Increased alkaline phosphatase	7	5
Increased lipase	6	17
Hypokalemia	3	4
Hyperkalemia	3	2
Decreased albumin	3	1
Increased creatinine	2	2
Hematology		
Thrombocytopenia	10	8
Lymphopenia	8	9
Neutropenia	7	3
Anemia	4	5
a	With at least 1 grade increase from baseline	
b	Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=278 to 470) and sorafenib (n=260 to 473)	

Endometrial Carcinoma

The safety of LENVIMA in combination with pembrolizumab was investigated in Study 309, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings [see *Clinical Studies (14.4)*]. Patients with endometrial carcinoma that are pMMR or not MSI-H received LENVIMA 20 mg orally once daily with pembrolizumab 200 mg intravenously every 3 weeks (n=342); or received doxorubicin or paclitaxel (n= 325).

For patients with pMMR or not MSI-H status, the median duration of study treatment was 7.2 months (range 1 day to 26.8 months) and the median duration of exposure to LENVIMA was 6.7 months (range: 1 day to 26.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency $\geq 3\%$ were hypertension (4.4%), and urinary tract infection (3.2%).

Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common ($\geq 1\%$) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%).

Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common ($\geq 5\%$) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and weight decreased (5%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common ($\geq 2\%$) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2%).

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in patients receiving LENVIMA in Study 309.

Table 11: Adverse Reactions in $\geq 20\%$ of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)				
	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Adverse Reaction	All Grades^a (%)	Grades 3-4 (%)	All Grades^a (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism ^b	67	0.9	0.9	0
Vascular				
Hypertension ^c	67	39	6	2.5
Hemorrhagic events ^d	25	2.6	15	0.9
General				
Fatigue ^e	58	11	54	6
Gastrointestinal				
Diarrhea ^f	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitis ^g	35	2.6	26	1.2
Abdominal pain ^h	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders ⁱ	53	5	27	0.6
Metabolism				
Decreased appetite ^j	44	7	21	0
Investigations				
Decreased weight	34	10	6	0.3
Renal and Urinary				
Proteinuria ^k	29	6	3.4	0.3
Infections				
Urinary tract infection ^l	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia ^m	23	2.9	0.9	0
Rash ⁿ	20	2.3	4.9	0

Table 11: Adverse Reactions in $\geq 20\%$ of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)				
	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Adverse Reaction	All Grades^a (%)	Grades 3-4 (%)	All Grades^a (%)	Grades 3-4 (%)
^a	Graded per NCI CTCAE v4.03			
^b	Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, and secondary hypothyroidism			
^c	Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, and blood pressure fluctuation			
^d	Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, injection site hemorrhage, melena, purpura, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, coital bleeding, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, and vessel puncture site bruise			
^e	Includes fatigue, asthenia, malaise, and lethargy			
^f	Includes diarrhea and gastroenteritis			
^g	Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, and tongue ulceration			
^h	Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, and epigastric discomfort			
ⁱ	Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw			
^j	Includes decreased appetite and early satiety			
^k	Includes proteinuria, protein urine present, hemoglobinuria			
^l	Includes urinary tract infection, cystitis, and pyelonephritis			
^m	Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, and skin reaction			
ⁿ	Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, and application site rash			

Table 12: Laboratory Abnormalities Worsened from Baseline^a Occurring in $\geq 20\%$ (All Grades) or $\geq 3\%$ (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)				
	Endometrial Carcinoma (pMMR or not MSI-H)			
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=342		Doxorubicin or Paclitaxel N=325	
Laboratory Test^b	All Grades^c (%)	Grades 3-4 (%)	All Grades^c (%)	Grades 3-4 (%)
Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	53	6	32	3.8
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.7
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Hematology				
Lymphopenia	50	16	65	20
Thrombocytopenia	50	8	30	4.7
Anemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	31	6	76	58
^a With at least 1 grade increase from baseline ^b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: LENVIMA/pembrolizumab (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients). ^c Graded per NCI CTCAE v4.03				

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LENVIMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: pancreatitis, increased amylase

General: impaired wound healing

Hepatobiliary: cholecystitis

Renal and Urinary: nephrotic syndrome

Vascular: arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Drugs That Prolong the QT Interval

LENVIMA has been reported to prolong the QT/QTc interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval [see *Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits (see *Data*). There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥ 0.3 mg/kg [approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose

level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma (*see Data*). Because of the potential for serious adverse reactions in breastfed children, advise women to discontinue breastfeeding during treatment with LENVIMA and for 1 week after the last dose.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher [based on area under the curve (AUC)] in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Based on animal data and its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating LENVIMA [*see Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

Infertility

LENVIMA may impair fertility in males and females of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of LENVIMA in pediatric patients have not been established.

Juvenile Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

8.5 Geriatric Use

Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in SELECT, 45% were ≥ 65 years of age and 11% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 352 patients with renal cell carcinoma (RCC) who received LENVIMA with pembrolizumab in CLEAR, 45% were ≥ 65 years of age and 13% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Of the 62 patients with RCC who received LENVIMA with everolimus in Study 205, 36% were ≥ 65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger subjects.

Of the 476 patients with hepatocellular carcinoma (HCC) who received LENVIMA in REFLECT, 44% were ≥ 65 years of age and 12% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between patients ≥ 65 and younger subjects. Patients ≥ 75 years of age showed reduced tolerability to LENVIMA.

Of 406 adult patients with endometrial carcinoma (EC) who were treated with LENVIMA in combination with pembrolizumab in Study 309, 201 (50%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose of lenvatinib for patients with RCC, DTC, or endometrial carcinoma and severe renal impairment [*see Dosage and Administration (2.7)*]. There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease [*see Warnings and Precautions (5.5), Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate or severe hepatic impairment.

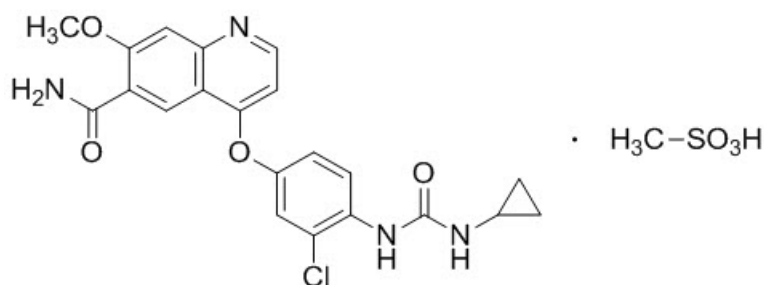
No dose adjustment is recommended for patients with DTC, RCC, or endometrial carcinoma and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose of lenvatinib for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment [see *Dosage and Administration* (2.7), *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable [see *Clinical Pharmacology* (12.3)]. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.

11 DESCRIPTION

LENVIMA, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(*N*⁷-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is C₂₁H₁₉ClN₄O₄ • CH₄O₃S, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pK_a value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.3.

LENVIMA capsules for oral administration contain 4 mg or 10 mg of lenvatinib, equivalent to 4.90 mg or 12.25 mg of lenvatinib mesylate, respectively. The inactive ingredients are: calcium carbonate, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and talc.

In addition, the capsule shell contains ferric oxide red, ferric oxide yellow, hypromellose, and titanium dioxide. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFR α), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2 α (FRS2 α) phosphorylation.

In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling in vitro, and by decreases in tumor volume in mouse xenograft models of human renal cell cancer that were greater than those with either drug alone.

12.2 Pharmacodynamics

Exposure-Response Relationships

In a multicenter randomized (1:1) double blind trial of 152 patients with radioactive iodine (RAI)-refractory DTC, a dose-response relationship for overall response rate (ORR) was observed over the dose range of 18 mg (0.75 times the recommended dose of 24 mg) and 24 mg. A higher ORR was observed at the recommended lenvatinib dose.

No dose-response relationships for adverse reactions, serious adverse reactions, adverse reactions leading to study drug discontinuation, and adverse reactions leading to study drug interruption were observed over the same dose range.

12.3 Pharmacokinetics

In patients with solid tumors administered single and multiple doses of LENVIMA once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 mg (0.1 times the recommended clinical dose of 24 mg) to 32 mg (1.33 times the recommended clinical dose of 24 mg) with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Geometric mean C_{max} and AUC values at steady state for RCC, DTC and HCC are summarized in the Table 13.

Tumor Type	Dose	Parameter	N	Geometric Mean	%CV
RCC	18 mg	C_{max} (ng/mL)	350	267	36.7
		AUC (ng·h/mL)	350	3148	42.5
	20 mg	C_{max} (ng/mL)	346	275	32.6
		AUC (ng·h/mL)	346	3135	41.3
DTC	24 mg	C_{max} (ng/mL)	251	323	33.3
		AUC (ng·h/mL)	251	3483	34.7
HCC (body weight < 60 kg)	8 mg	C_{max} (ng/mL)	150	154	25.4
		AUC (ng·h/mL)	150	1835	34.0
HCC (body weight ≥ 60 kg)	12 mg	C_{max} (ng/mL)	318	172	23.1
		AUC (ng·h/mL)	318	2013	29.3

^a Model-predicted steady-state pharmacokinetic parameters are presented.

Absorption

The time to peak plasma concentration (T_{\max}) typically occurred from 1 to 4 hours post-dose.

Food Effect

Administration with a high fat meal (approximately 900 calories of which approximately 55% were from fat, 15% from protein, and 30% from carbohydrates) did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{\max} from 2 hours to 4 hours.

Distribution

Model-predicted geometric mean steady state volume of distribution is 97 L (%CV, 30.2%). Protein binding of lenvatinib is 97% to 99%, which is independent of concentration, and is not impacted by hepatic or renal function. The blood-to-plasma concentration ratio ranged from 0.59 to 0.61 at concentrations of 0.1 to 10 $\mu\text{g/mL}$ in vitro.

Elimination

The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion

Ten days after a single administration of radiolabeled lenvatinib, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Specific Populations

Age (18 to 92 years), sex, race/ethnicity (White, Black and Asian), tumor types (DTC, RCC, HCC and other tumor types) and renal impairment (creatinine clearance: 15-89 mL/min) did not have a significant effect on apparent oral clearance (CL/F). Subjects with end stage renal disease were not studied.

Patients with Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose were evaluated in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $\text{AUC}_{0-\text{inf}}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively.

Apparent oral clearance of lenvatinib in patients with HCC and mild hepatic impairment was similar to patients with HCC and moderate hepatic impairment.

Body Weight

Lenvatinib exposures in patients with HCC in REFLECT were comparable between those weighing <60 kg who received a starting dose of 8 mg and those ≥ 60 kg who received a starting dose of 12 mg.

Drug Interaction Studies

Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors: Ketoconazole (400 mg daily for 18 days) increased lenvatinib (administered as a single 5 mg dose on Day 5) AUC by 15% and C_{max} by 19%.

P-gp Inhibitor: Rifampicin (600 mg as a single dose) increased lenvatinib (24 mg as a single dose) AUC by 31% and C_{max} by 33%.

CYP3A and P-gp Inducers: Rifampicin (600 mg daily for 21 days) decreased lenvatinib (24 mg as a single dose on Day 15) AUC by 18%. The C_{max} was unchanged.

Population pharmacokinetic analysis demonstrated that neither everolimus nor pembrolizumab meaningfully affect the pharmacokinetics of lenvatinib.

In Vitro Studies with Transporters: Lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion (MATE) 1, MATE2-K, or the bile salt export pump (BSEP).

Effect of Lenvatinib on Other Drugs

CYP2C8 Substrate: There is no projected significant drug-drug interaction risk between lenvatinib and repaglinide.

CYP3A4 Substrate: Co-administration of lenvatinib with midazolam had no effect on the pharmacokinetics of midazolam.

Population pharmacokinetic analysis demonstrated that lenvatinib does not meaningfully affect the pharmacokinetics of either everolimus or pembrolizumab.

In Vitro Studies with Substrates of CYP or UDP-glucuronosyltransferase (UGT): Lenvatinib inhibits CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Lenvatinib does not inhibit CYP2A6 and CYP2E1. Lenvatinib induces CYP3A, but it does not induce CYP1A1, CYP1A2, CYP2B6, and CYP2C9.

Lenvatinib inhibits UGT1A1, UGT1A4, and UGT1A9 in vitro, but likely only inhibits UGT1A1 in vivo in the gastrointestinal tract based on the expression of the enzyme in tissues. Lenvatinib does not inhibit UGT1A6, UGT2B7 or aldehyde oxidase. Lenvatinib does not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

In Vitro Studies with Substrates of Transporters:

Lenvatinib does not have the potential to inhibit MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, BSEP, OATP1B1, or OATP1B3 in vivo.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib mesylate was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the in vitro mouse lymphoma thymidine kinase assay or the in vivo rat micronucleus assay.

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular

hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the AUC at the recommended clinical dose of 24 mg once daily. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the AUC at the recommended clinical dose of 24 mg once daily, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at lenvatinib exposures lower than those observed in humans at the recommended clinical dose of 24 mg once daily.

14 CLINICAL STUDIES

14.1 Differentiated Thyroid Cancer

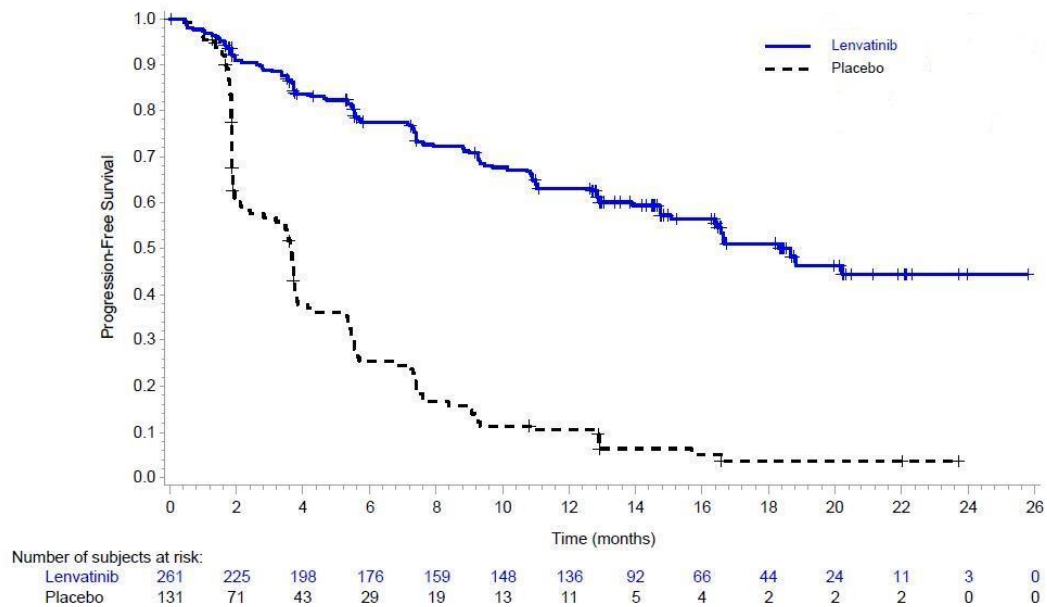
A multicenter, randomized (2:1), double-blind, placebo-controlled study (SELECT; NCT01321554) was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Radioactive iodine (RAI)-refractory was defined as 1 or more measurable lesions with no iodine uptake on RAI scan, iodine uptake with progression within 12 months of RAI therapy, or having received cumulative RAI activity >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic region, prior VEGF/VEGFR-targeted therapy, and age. The major efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Independent review confirmation of disease progression was required prior to discontinuing patients from the randomization phase of the study. Other efficacy outcome measures included objective response rate (ORR) and overall survival (OS). Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression.

Of the 392 patients randomized, 51% were male, the median age was 63 years, 40% were 65 years or older, 79% were White, 54% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, and 24% had received 1 prior VEGF/VEGFR-targeted therapy. Metastases were present in 99% of the patients: lungs in 89%, lymph nodes in 52%, bone in 39%, liver in 18%, and brain in 4%. The histological diagnoses were papillary thyroid cancer (66%) and follicular thyroid cancer (34%); of those with follicular histology, 44% had Hürthle cell and 11% had clear cell subtypes. In the LENVIMA arm, 67% of patients did not demonstrate iodine uptake on any RAI scan compared to 77% in the placebo arm. Additionally, 59% of patients on the LENVIMA arm and 61% of patients on placebo arm progressed, according to RECIST 1.1, within 12 months of prior I 131 therapy; 19.2% of patients on the LENVIMA arm and 17.6% of patients on placebo arm received prior cumulative activity of >600 mCi or 22 GBq I 131, with the last dose administered at least 6 months prior to study entry. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo (Table 14 and Figure 1). Upon confirmation of progression, 83% of patients that were randomly assigned to placebo crossed over to receive open-label LENVIMA.

Table 14: Efficacy Results in Differentiated Thyroid Cancer in SELECT		
	LENVIMA N=261	Placebo N=131
Progression-Free Survival (PFS)^a		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI) ^b	0.21 (0.16, 0.28)	
P-value ^c	<0.001	
Objective Response Rate^a		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value ^d	<0.001	
Overall Survival (OS)^e		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI) ^b	0.73 (0.50, 1.07)	
P-value ^b	0.10	
<p>a Independent radiologic review</p> <p>b Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)</p> <p>c Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)</p> <p>d Cochran-Mantel-Haenszel chi-square test</p> <p>e NE = Not estimable</p>		

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in SELECT



14.2 Renal Cell Carcinoma

First-Line Treatment of Patients with RCC in Combination with Pembrolizumab (CLEAR)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in CLEAR (NCT02811861), a multicenter, open-label, randomized trial that enrolled 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America and Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate and poor risk).

Patients were randomized (1:1:1) to one of the following treatment arms:

- LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks up to 24 months.
- LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

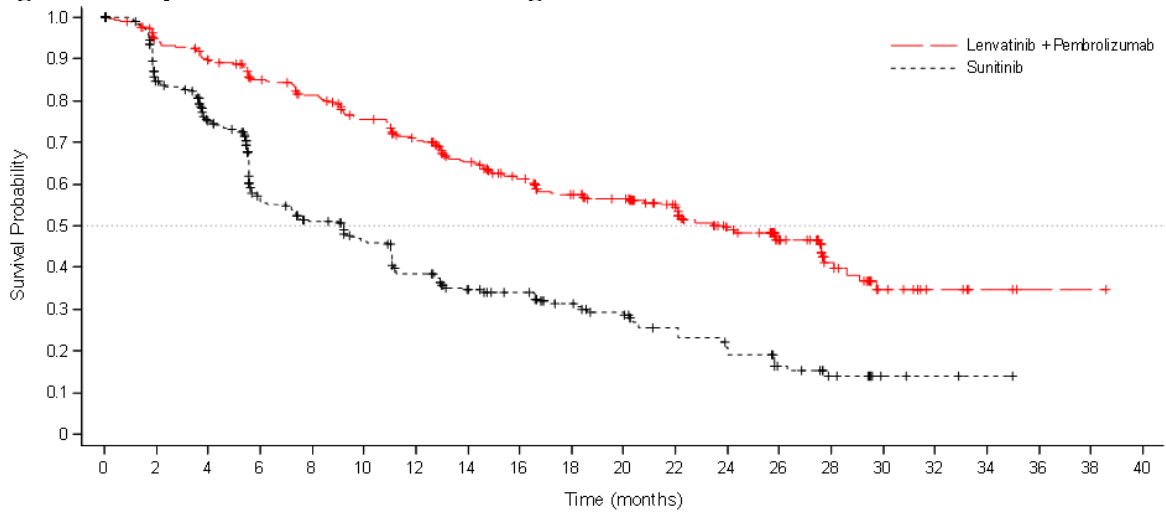
Treatment continued until unacceptable toxicity or disease progression. Administration of LENVIMA with pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab dosing was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years); 42% age 65 or older, 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC. LENVIMA in combination with pembrolizumab demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. Table 15 and Figures 2 and 3 summarize the efficacy results for CLEAR.

Table 15: Efficacy Results in Renal Cell Carcinoma Per IRC in CLEAR		
	LENVIMA20 mg with Pembrolizumab 200mg N=355	Sunitinib 50mg N=357
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45%)	205 (57%)
Progressive disease	145 (41%)	196 (55%)
Death	15 (4%)	9 (3%)
Median PFS in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard Ratio ^a (95% CI)	0.39 (0.32, 0.49)	
p-value ^b	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (23%)	101 (28%)
Median OS in months (95% CI)	NR (33.6, NE)	NR (NE, NE)
Hazard Ratio ^a (95% CI)	0.66 (0.49, 0.88)	
p-value ^b	0.0049	
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	252 (71%)	129 (36%)
(95% CI)	(66, 76)	(31, 41)
Complete response rate	16%	4%
Partial responses rate	55%	32%
p-value ^c	<0.0001	
Tumor assessments were based on RECIST 1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020 CI = confidence interval; NE= Not estimable; NR= Not reached		
a Hazard ratio is based on a Cox Proportional Hazards Model, stratified by geographic region and MSKCC prognostic groups.		
b Two-sided p-value based on stratified log-rank test.		
c Two-sided p-value based upon CMH test.		

Figure 2: Kaplan-Meier Curves for Progression-Free Survival in CLEAR

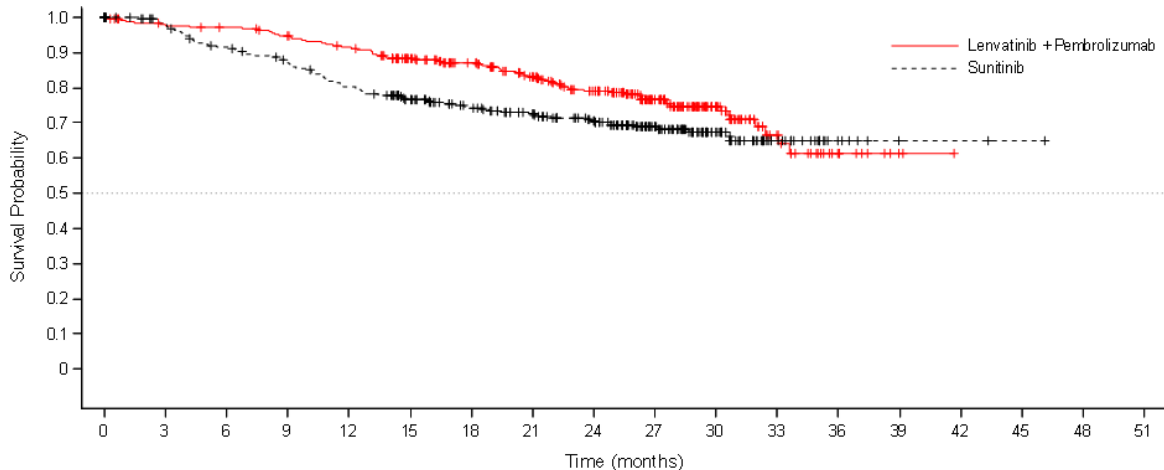


Number of subjects at risk:

L+P	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
S	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.

Figure 3: Kaplan-Meier Curves for Overall Survival in CLEAR



Number of subjects at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
L+P	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0			
S	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0	

L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.

Previously Treated RCC in Combination with Everolimus (Study 205)

The efficacy was evaluated in a multicenter, randomized (1:1:1) study (Study 205: NCT01136733), in which 153 patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy received LENVIMA 18 mg orally once daily with everolimus 5 mg orally once daily, LENVIMA 24 mg orally once daily, or everolimus 10 mg orally once daily. Patients were required to have histological confirmation of clear cell RCC and ECOG PS of 0 or 1. Patients were stratified by hemoglobin level (\leq or >13 g/dL for males and \leq or >11.5 g/dL for females) and corrected serum calcium (≥ 10 mg/dL vs. <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST 1.1.

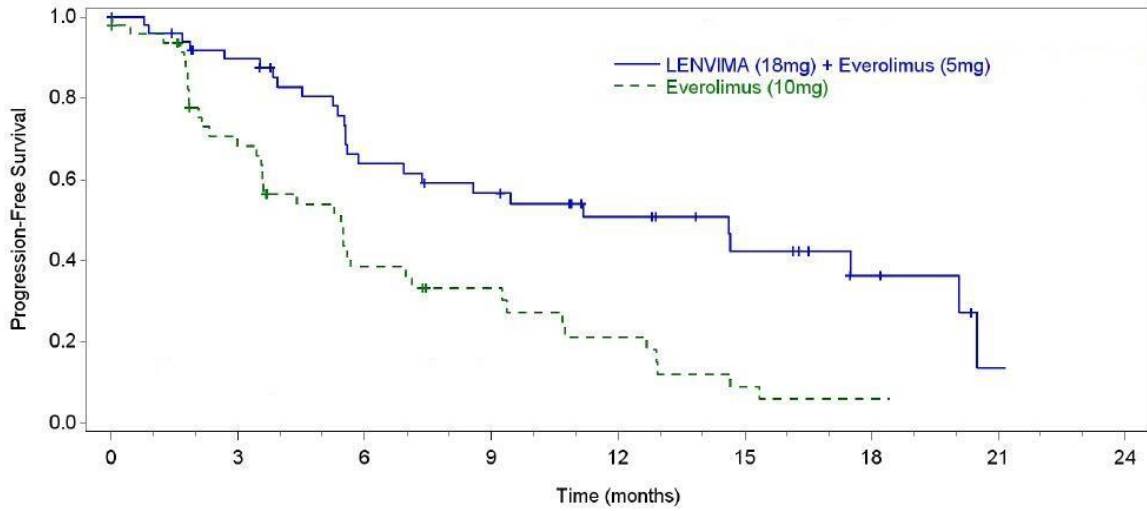
Of the 101 patients randomized to the LENVIMA with everolimus arm or everolimus arm, 72% were male, the median age was 60 years, 31% were older than 65 years, and 96% were White. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across these two treatment arms. MSKCC favorable, intermediate, and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA with everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

Efficacy results from Study 205 are summarized in Table 16 and Figures 4 and 5. The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm.

Table 16: Efficacy Results in Renal Cell Carcinoma Per Investigator Assessment in Study 205

	LENVIMA 18 mg with Everolimus 5 mg N=51	Everolimus 10 mg N=50
Progression-Free Survival (PFS)^a		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI) ^b LENVIMA with Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival (OS)^c		
Number of deaths, n (%)	32 (63)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI) ^b LENVIMA with Everolimus vs Everolimus	0.67 (0.42, 1.08)	-
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	19 (37)	3 (6)
(95% CI)	(24, 52)	(1, 17)
Number of complete responses, n (%)	1 (2)	0
Number of partial responses (%)	18 (35)	3 (6)
Tumor assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR. Data cutoff date = 13 Jun 2014		
CI = confidence interval		
a Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.		
b Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata.		
c Data cutoff date = 31 Jul 2015		

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Study 205

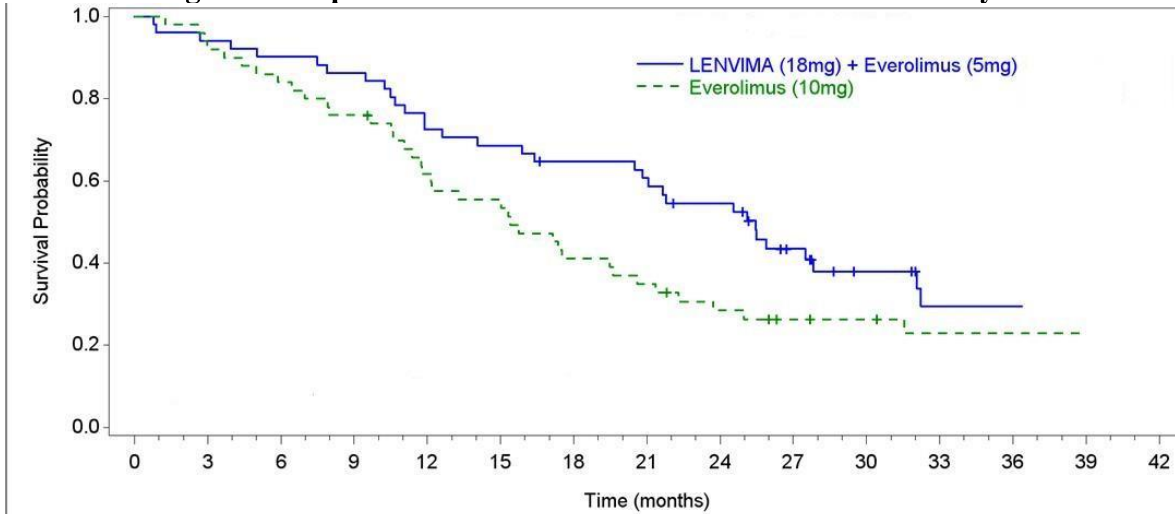


Number of Subjects at risk:

L(18mg) + E(5mg)	51	41	27	23	16	10	5	1	0
E(10mg)	50	29	15	11	7	3	1	0	

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 13JUN2014

Figure 5: Kaplan-Meier Curves for Overall Survival in Study 205



Number of Subjects at risk:

L(18mg) + E(5mg)	51	48	46	44	37	35	32	30	26	17	11	7	2	0	0
E(10mg)	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 31JUL2015

14.3 Hepatocellular Carcinoma

The efficacy of LENVIMA was evaluated in a randomized, open-label, multicenter, international study (REFLECT; NCT01761266) conducted in patients with previously untreated unresectable hepatocellular carcinoma (HCC). The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) Stage C or B HCC who were ineligible for local liver-directed therapy; had an ECOG PS of 0 or 1; had received no prior systemic therapy for HCC; and had at least one measurable target lesion according to modified RECIST for HCC.

Patients were randomized (1:1) to receive LENVIMA (12 mg for baseline body weight ≥ 60 kg or 8 mg for baseline body weight < 60 kg) orally once daily or sorafenib 400 mg orally twice daily until radiological disease progression or unacceptable toxicity. Randomization was stratified by region (Western vs Asia Pacific), presence of macroscopic portal vein invasion or extrahepatic spread (yes vs no), ECOG PS (0 vs 1), and body weight (< 60 kg vs ≥ 60 kg). The major efficacy outcome measure was overall survival (OS). REFLECT was designed to show the non-inferiority of LENVIMA to sorafenib for OS. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR) according to modified RECIST for HCC.

A total of 954 patients were randomized, 478 to the LENVIMA arm and 476 to the sorafenib arm. The demographics of the study population were: median age of 62 years (range: 20 to 88 years); 84% male; 69% Asian and 29% White; 63% ECOG PS of 0; and 69% weighed ≥ 60 kg. Of the 590 (62%) patients with at least one site of documented distant metastatic disease, 52% had lung metastasis, 45% had lymph node metastasis, and 16% had bone metastasis.

Macroscopic portal vein invasion, extra-hepatic spread, or both were present in 70% of patients. HCC was categorized as Child-Pugh A and BCLC Stage C in 79% and Child-Pugh A and BCLC Stage B in 21% of patients. Seventy-five percent (75%) of patients had radiographic evidence of cirrhosis at baseline. Investigator-documented primary risk factors for the development of HCC were hepatitis B (50%), hepatitis C (23%), alcohol use (6%), other (7%), and unknown (14%).

REFLECT demonstrated that LENVIMA was non-inferior to sorafenib for OS. REFLECT did not demonstrate a statistically significant improvement in OS for patients randomized to LENVIMA as compared to those in the sorafenib arm. LENVIMA was statistically significantly superior to sorafenib for PFS and ORR. Efficacy results are summarized in Table 17 and Figure 6.

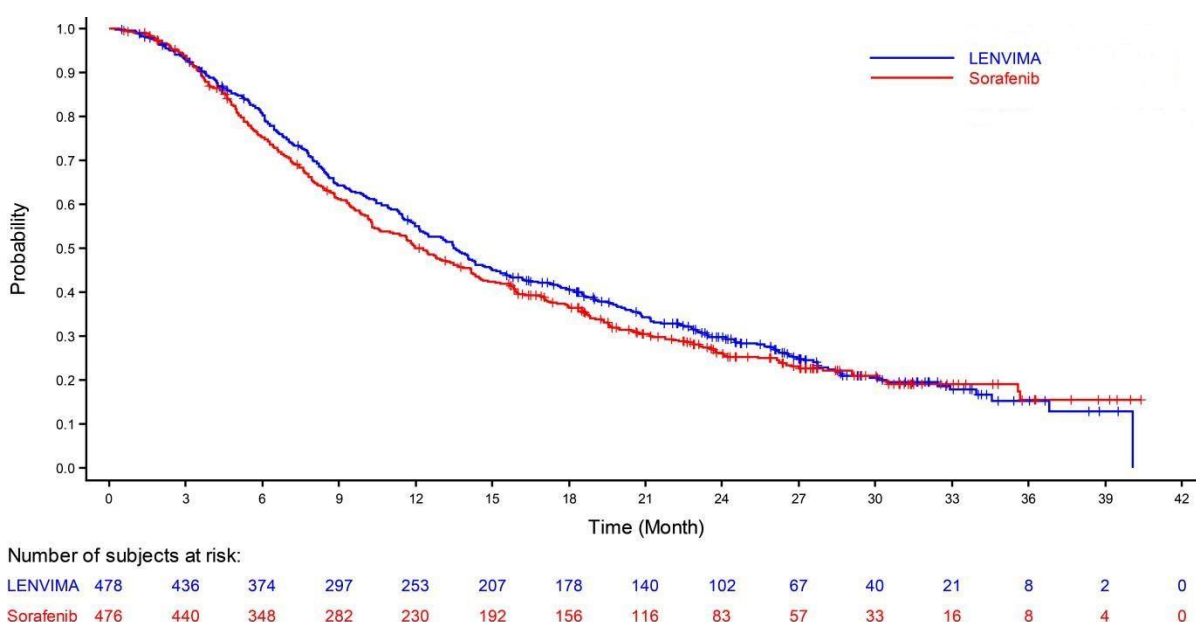
Table 17: Efficacy Results in Hepatocellular Carcinoma in REFLECT		
	LENVIMA N= 478	Sorafenib N=476
Overall Survival		
Number of deaths (%)	351 (73)	350 (74)
Median OS in months (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Hazard Ratio (95% CI) ^a	0.92 (0.79, 1.06)	
Progression-Free Survival^b (mRECIST)		
Number of Events (%)	311 (65)	323 (68)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Hazard Ratio (95% CI)	0.64 (0.55, 0.75)	
P-value	<0.001	
Objective Response Rate^b (mRECIST)		
Objective response rate	41%	12%
Complete responses, n (%)	10 (2.1)	4 (0.8)
Partial responses, n (%)	184 (38.5)	55 (11.6)
95% CI	(36%, 45%)	(10%, 16%)
P-value	<0.001	
Progression-Free Survival^b (RECIST 1.1)		
Number of Events (%)	307 (64)	320 (67)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.9)
Hazard Ratio (95% CI)	0.65 (0.56, 0.77)	
Objective Response Rate^b (RECIST 1.1)		
Objective response rate	19%	7%
Complete responses, n (%)	2 (0.4)	1 (0.2)
Partial responses, n (%)	88 (18.4)	30 (6.3)
95% CI	(15%, 22%)	(4%, 9%)

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; OS = overall survival.

a Based on stratified Cox-model. Non-inferiority margin for HR (lenvatinib vs sorafenib) is 1.08.

b Per independent radiology review.

Figure 6: Kaplan-Meier Curves for Overall Survival in REFLECT



14.4 Endometrial Carcinoma (EC)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in Study 309 (NCT03517449), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were pMMR (using the VENTANA MMR RxDx Panel test) or not MSI-H were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks.
- Investigator's choice consisting of either doxorubicin 60 mg/m² every 3 weeks, or paclitaxel 80 mg/m² given weekly, 3 weeks on/1 week off.

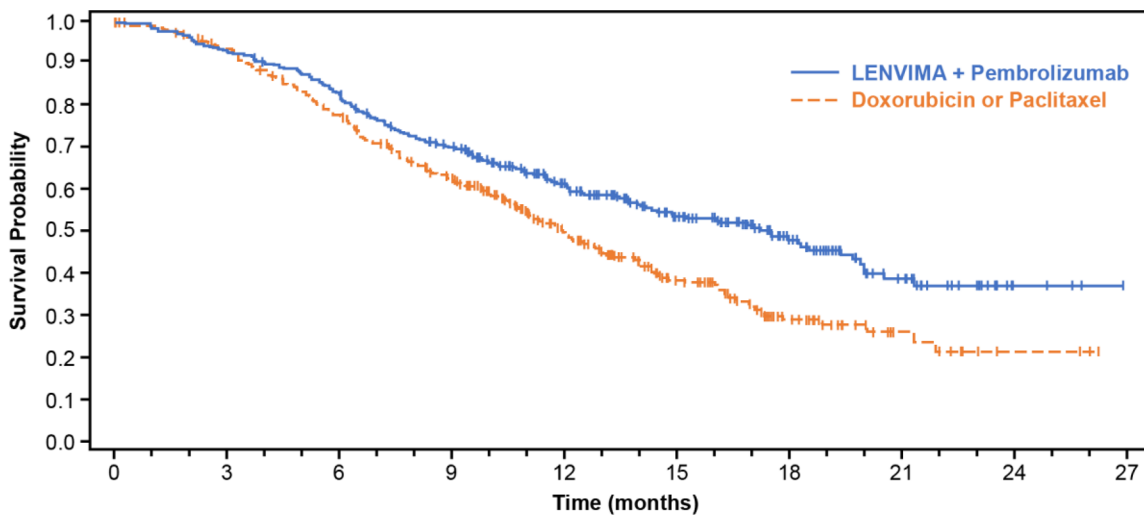
Treatment with LENVIMA and pembrolizumab continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DOR, as assessed by BICR.

Among the 697 pMMR or not MSI-H patients, 346 patients were randomized to LENVIMA in combination with pembrolizumab, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The population characteristics of these patients were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

Efficacy results for these patients are summarized in Table 18 and Figures 7 and 8.

Table 18: Efficacy Results in Endometrial Carcinoma in Study 309		
	Endometrial Carcinoma (pMMR or not MSI-H)	
Endpoint	LENVIMA with pembrolizumab N=346	Doxorubicin or Paclitaxel N=351
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio ^a (95% CI)	0.68 (0.56, 0.84)	
p-Value ^b	0.0001	
PFS^c		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio ^a (95% CI)	0.60 (0.50, 0.72)	
p-Value ^b	<0.0001	
Objective Response Rate		
ORR ^c (95% CI)	30% (26, 36)	15% (12,19)
Complete response	5%	3%
Partial response	25%	13%
p-Value ^d	<0.0001	
Duration of Response	N=105	N=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)
^a Based on the stratified Cox regression model		
^b Based on stratified log-rank test		
^c Per independent radiology review		
^d Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation		

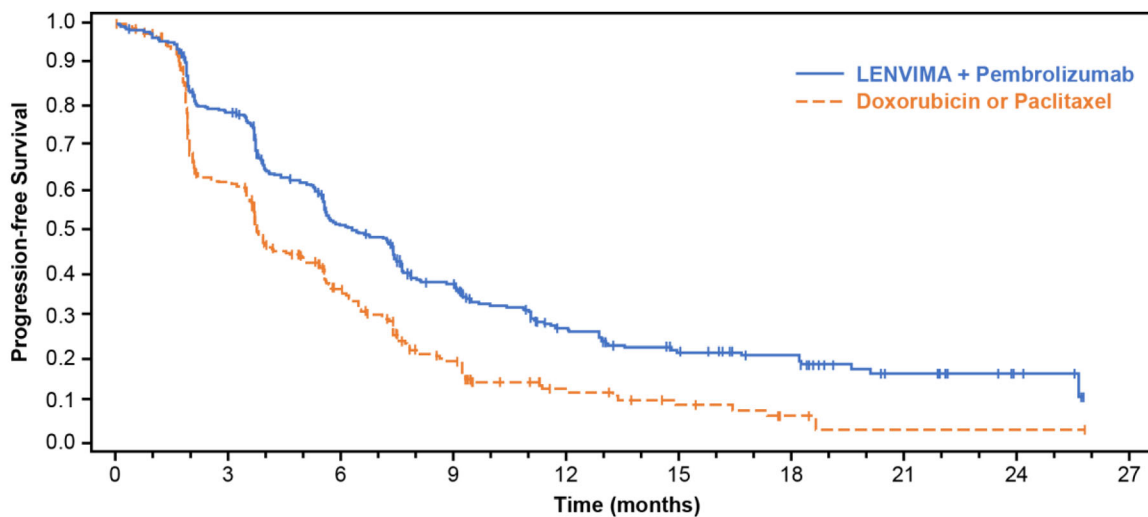
Figure 7: Kaplan-Meier Curves for Overall Survival in Study 309 (pMMR or not MSI-H)



Number of subjects at risk:

	0	3	6	9	12	15	18	21	24	27
LENVIMA + Pembrolizumab	346	322	285	232	160	109	62	28	5	0
Doxorubicin or Paclitaxel	351	319	262	201	120	70	33	11	3	0

Figure 8: Kaplan-Meier Curves for Progression-Free Survival in Study 309 (pMMR or not MSI-H)



Number of subjects at risk:

	0	3	6	9	12	15	18	21	24	27
LENVIMA + Pembrolizumab	346	264	165	112	60	39	30	12	5	0
Doxorubicin or Paclitaxel	351	177	83	37	15	8	3	1	1	0

16 HOW SUPPLIED/STORAGE AND HANDLING

LENVIMA 4 mg capsules are supplied as hard hypromellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with “C” on the cap and “LENV 4 mg” on the body.

LENVIMA 10 mg capsules are supplied as hard hypromellose capsules with yellow body and yellowish-red cap, marked in black ink with “C” on the cap and “LENV 10 mg” on the body.

LENVIMA capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card as follows:

- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-718-30: 18 mg, carton with 6 cards NDC 62856-718-05 (five 10 mg capsules and ten 4 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-712-30: 12 mg, carton with 6 cards NDC 62856-712-05 (fifteen 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).
- NDC 62856-708-30: 8 mg, carton with 6 cards NDC 62856-708-05 (ten 4 mg capsules per card).
- NDC 62856-704-30: 4 mg, carton with 6 cards NDC 62856-704-05 (five 4 mg capsules per card).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension

Advise patients to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated [see *Warnings and Precautions (5.1)*].

Cardiac Dysfunction

Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction [see *Warnings and Precautions (5.2)*].

Arterial Thrombotic Events

Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke [see *Warnings and Precautions (5.3)*].

Hepatotoxicity

Advise patients that they will need to undergo laboratory tests to monitor liver function and to report any new symptoms indicating hepatic toxicity or failure [see *Warnings and Precautions* (5.4)].

Proteinuria and Renal Failure/Impairment

Advise patients that they will need to undergo regular laboratory tests to monitor kidney function and protein in the urine [see *Warnings and Precautions* (5.5, 5.6)].

Diarrhea

Advise patients when to start standard anti-diarrheal therapy and to maintain adequate hydration. Advise patients to contact their healthcare provider if they are unable to maintain adequate hydration [see *Warnings and Precautions* (5.7)].

Fistula Formation and Gastrointestinal Perforation

Advise patients that LENVIMA can increase the risk of fistula formation or gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain [see *Warnings and Precautions* (5.8)].

QTc Interval Prolongation

Advise patients who are at risk for QTc prolongation that they will need to undergo regular ECGs. Advise all patients that they will need to undergo laboratory tests to monitor electrolytes [see *Warnings and Precautions* (5.9)].

Hypocalcemia

Advise patients of the risks of hypocalcemia, that they will need to undergo laboratory tests to monitor calcium levels, and the potential requirement for calcium supplementation [see *Warnings and Precautions* (5.10)].

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Advise patients of the signs and symptoms of RPLS and to contact their healthcare provider for new onset or worsening neurological function [see *Warnings and Precautions* (5.11)].

Hemorrhagic Events

Advise patients that LENVIMA can increase the risk for bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding [see *Warnings and Precautions* (5.12)].

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

Advise patients that LENVIMA can cause hypothyroidism and that their thyroid function should be monitored regularly during treatment [see *Warnings and Precautions* (5.13)].

Impaired Wound Healing

Advise patients that LENVIMA may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see *Warnings and Precautions* (5.14)].

Osteonecrosis of the Jaw (ONJ)

Advise patients regarding good oral hygiene practices and to have preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Inform patients being treated with LENVIMA, particularly those who are at high risk for ONJ, to avoid invasive dental procedures, if possible, and to inform their healthcare provider of any planned dental procedures [see *Warnings and Precautions (5.15)*]. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with ONJ.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.16)*, *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose [see *Use in Specific Populations (8.3)*].

Lactation

Advise women to discontinue breastfeeding during treatment with LENVIMA and for 1 week after the last dose [see *Use in Specific Populations (8.2)*].

Distributed by:

Eisai Inc.

Nutley, NJ 07110

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PATIENT INFORMATION
LENVIMA® (lehn-veema)
(lenvatinib)
capsules

What is LENVIMA?

LENVIMA is a prescription medicine that is used to treat people with certain kinds of cancer.

- LENVIMA is used by itself to treat differentiated thyroid cancer (DTC), a type of thyroid cancer that can no longer be treated with radioactive iodine and is progressing.
- LENVIMA is used to treat adults with a type of kidney cancer called advanced renal cell carcinoma (RCC):
 - along with the medicine pembrolizumab as your first treatment when your kidney cancer has spread or cannot be removed by surgery.
 - along with the medicine everolimus after one course of treatment with another anti-cancer medicine.
- LENVIMA is used by itself as the first treatment for a type of liver cancer called hepatocellular carcinoma (HCC) when it cannot be removed by surgery.
- LENVIMA is used along with another medicine called pembrolizumab to treat advanced endometrial carcinoma (EC), a type of uterine cancer:
 - when a laboratory test shows that your tumor is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), **and**
 - you have received anti-cancer treatment, and it is no longer working, **and**
 - your cancer cannot be cured by surgery or radiation.

It is not known if LENVIMA is safe and effective in children.

Before you take LENVIMA, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have heart problems
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack, or change in vision
- have or have had liver or kidney problems
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two or more body parts (fistula)
- have headaches, seizures, or vision problems
- have any bleeding problems
- plan to have surgery, a dental procedure, or have had a recent surgery. You should stop taking LENVIMA at least 1 week before planned surgery. See **“What are the possible side effects of LENVIMA?”**
- are pregnant or plan to become pregnant. LENVIMA can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with LENVIMA.
- You should use an effective method of birth control during treatment with LENVIMA and for 30 days after the last dose of LENVIMA. Talk with your healthcare provider about birth control methods you can use during this time. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with LENVIMA.
- are breastfeeding or plan to breastfeed. It is not known if LENVIMA passes into your breast milk. Do not breastfeed during treatment with LENVIMA and for 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you are taking, or have taken, an osteoporosis medicine.

Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take LENVIMA?

- Take LENVIMA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much LENVIMA to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with LENVIMA if you have side effects.
- Take LENVIMA 1 time each day at the same time, with or without food.
- If you miss a dose of LENVIMA, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.
- Swallow LENVIMA capsules whole. Do not crush or chew the LENVIMA capsules.
- If you cannot swallow LENVIMA capsules whole, LENVIMA capsules can be mixed with water or apple juice, then taken by mouth, or mixed with water and given through a feeding tube.

How to take LENVIMA by mouth if you cannot swallow whole capsules:

- Place your daily dose, up to 5 capsules, in a small container or oral syringe (approximately 20 mL capacity).
- Add 3 mL of **water or apple juice** to the container or oral syringe. **Wait 10 minutes** for the capsule shell (outer surface) to dissolve completely, then stir or shake the mixture for 3 minutes until capsules are fully dissolved. Do not break or crush the capsules.
- Drink the liquid mixture or use an oral syringe to take directly into the mouth.
- Next, using a second syringe, add an additional 2 mL of liquid to the container or oral syringe (cap the first oral syringe before adding the additional water) then swirl or shake and take the liquid mixture. Repeat this step at least one time and until you cannot see any of the LENVIMA mixture left in the container or oral syringe to make sure all of the medicine is taken.
- If 6 capsules are required for your daily dose, follow the above instructions using 3 capsules at a time.

How to give LENVIMA through a feeding tube:

- LENVIMA should be given in feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).
 - Place your daily dose, up to 5 capsules, in a syringe (20 mL capacity).
 - Add 3 mL of **water** to the syringe. **Wait 10 minutes** for the capsule shell (outer surface) to dissolve completely, then stir or shake the mixture for 3 minutes until capsules are fully dissolved. Do not break or crush the capsules.
 - Give the mixture through a feeding tube.
 - Next, cap the syringe and remove the plunger. Use a second syringe and add an additional 2 mL of liquid to the syringe. Swirl or shake and give the mixture in the feeding tube. Repeat this step at least one time and until you cannot see any of the LENVIMA mixture left in the syringe to make sure all of the medicine is taken.
 - If 6 capsules are required for your daily dose, follow the above instructions using 3 capsules at a time.
- LENVIMA mixture may be stored in a covered container in the refrigerator at 36°F to 46°F (2°C to 8°C) for a maximum of 24 hours. Throw away the LENVIMA mixture if not used within 24 hours of mixing.
- If you take too much LENVIMA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of LENVIMA?

LENVIMA may cause serious side effects, including:

- **High blood pressure (hypertension).** High blood pressure is a common side effect of LENVIMA and can be serious. Your blood pressure should be well controlled before you start taking LENVIMA. Your healthcare provider should check your blood pressure regularly during treatment with LENVIMA. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure.
- **Heart problems.** LENVIMA can cause serious heart problems that may lead to death. Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **Problem with blood clots in your blood vessels (arteries).** Get emergency medical help right away if you get any of the following symptoms:

- severe chest pain or pressure
- pain in your arms, back, neck or jaw
- shortness of breath
- numbness or weakness on one side of your body
- trouble talking
- sudden severe headache
- sudden vision changes

- **Liver problems.** LENVIMA may cause liver problems that may lead to liver failure and death. Your healthcare provider will check your liver function before and during treatment with LENVIMA. Tell your healthcare provider right away if you have any of the following symptoms:
 - your skin or the white part of your eyes turns yellow (jaundice)
 - dark “tea colored” urine
 - light-colored bowel movements (stools)
 - feeling drowsy, confused or loss of consciousness
- **Kidney problems.** Kidney failure, which can lead to death, has happened with LENVIMA treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **Increased protein in your urine (proteinuria).** Proteinuria is a common side effect of LENVIMA and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with LENVIMA.
- **Diarrhea.** Diarrhea is a common side effect of LENVIMA and can be serious. If you get diarrhea, ask your healthcare provider about what medicines you can take to treat your diarrhea. It is important to drink more water when you get diarrhea. Tell your healthcare provider or go to the emergency room if you are unable to drink enough liquids and your diarrhea is not able to be controlled.
- **An opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (fistula).** Get emergency medical help right away if you have severe stomach (abdomen) pain.
- **Changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider will do blood tests before and during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood, and may check the electrical activity of your heart with an ECG.
- **Low levels of blood calcium (hypocalcemia).** Your healthcare provider will check your blood calcium levels during treatment with LENVIMA and may tell you to take a calcium supplement if your calcium levels are low.
- **A condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get severe headache, seizures, weakness, confusion, or blindness or change in vision.
- **Bleeding.** LENVIMA may cause serious bleeding problems that may lead to death. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with LENVIMA, including:
 - severe and persistent nose bleeds
 - vomiting blood
 - red or black (looks like tar) stools
 - blood in your urine
 - coughing up blood or blood clots
 - heavy or new onset vaginal bleeding
- **Change in thyroid hormone levels.** Your healthcare provider should check your thyroid hormone levels before starting and every month during treatment with LENVIMA.
- **Wound healing problems.** Wound healing problems have happened in some people who take LENVIMA. Tell your healthcare provider if you plan to have any surgery before or during treatment with LENVIMA.
 - You should stop taking LENVIMA at least 1 week before planned surgery.
 - Your healthcare provider should tell you when you may start taking LENVIMA again after surgery.
- **Severe jawbone problems (osteonecrosis).** Severe jawbone problems have happened in some people who take LENVIMA. Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jawbone problems. Your healthcare provider should examine your mouth before you start and during treatment with LENVIMA. Tell your dentist that you are taking LENVIMA. It is important for you to practice good mouth care during treatment with LENVIMA. Tell your healthcare provider right away if you get signs or symptoms of jawbone problems during treatment with LENVIMA, including jaw pain, toothache, or sores on your gums. Tell your healthcare provider if you plan to have any dental procedures before or during treatment with LENVIMA. You should avoid having

invasive dental procedures if possible, during treatment with LENVIMA. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.

- You should stop taking LENVIMA at least 1 week before planned dental surgery or invasive dental procedures.
- Your healthcare provider should tell you when you may start taking LENVIMA again after dental procedures.

The most common side effects of LENVIMA in people treated for thyroid cancer include:

- tiredness
- joint and muscle pain
- decreased appetite
- weight loss
- nausea
- mouth sores
- headache
- vomiting
- rash, redness, itching, or peeling of your skin on your hands and feet
- stomach (abdomen) pain
- hoarseness

The most common side effects of LENVIMA when given with everolimus include:

- tiredness
- joint and muscle pain
- decreased appetite
- vomiting
- nausea
- mouth sores
- swelling in your arms and legs
- cough
- stomach (abdomen) pain
- trouble breathing
- rash
- weight loss
- bleeding

The most common side effects of LENVIMA in people treated for liver cancer include:

- tiredness
- decreased appetite
- joint and muscle pain
- weight loss
- stomach (abdomen) pain
- rash, redness, itching, or peeling of your skin on your hands and feet
- hoarseness
- bleeding
- change in thyroid hormone levels
- nausea

The most common side effects of LENVIMA when given with pembrolizumab include:

- decrease in thyroid hormone levels
- increased blood pressure
- tiredness
- diarrhea
- joint and muscle pain
- nausea
- decreased appetite
- vomiting
- mouth sores
- weight loss
- stomach-area (abdomen) pain
- urinary tract infection
- protein in your urine
- constipation
- headache
- bleeding
- rash, redness, itching, or peeling of your skin on your hands and feet
- hoarseness
- rash

LENVIMA may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Your healthcare provider may need to reduce your dose of LENVIMA, or delay or completely stop treatment, if you have certain side effects.

These are not all the possible side effects of LENVIMA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LENVIMA?

- Store LENVIMA at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep LENVIMA and all medicines out of the reach of children.**

General information about the safe and effective use of LENVIMA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LENVIMA for a condition for which it was not prescribed. Do not give LENVIMA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about LENVIMA that is written for health professionals.

What are the ingredients in LENVIMA?

Active ingredient: lenvatinib

Inactive ingredients: calcium carbonate, hydroxypropyl cellulose, low-substituted hydroxypropylcellulose, mannitol, microcrystalline cellulose, and talc.

The capsule shell contains: hypromellose, titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol and shellac.

Distributed by: Eisai Inc., Nutley, NJ 07110

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For more information, call 1-877-873-4724 or go to www.LENVIMA.com.

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This Patient Information has been approved by the U.S. Food and Drug Administration.

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